ANNALS OF INTERNAL MEDICINE

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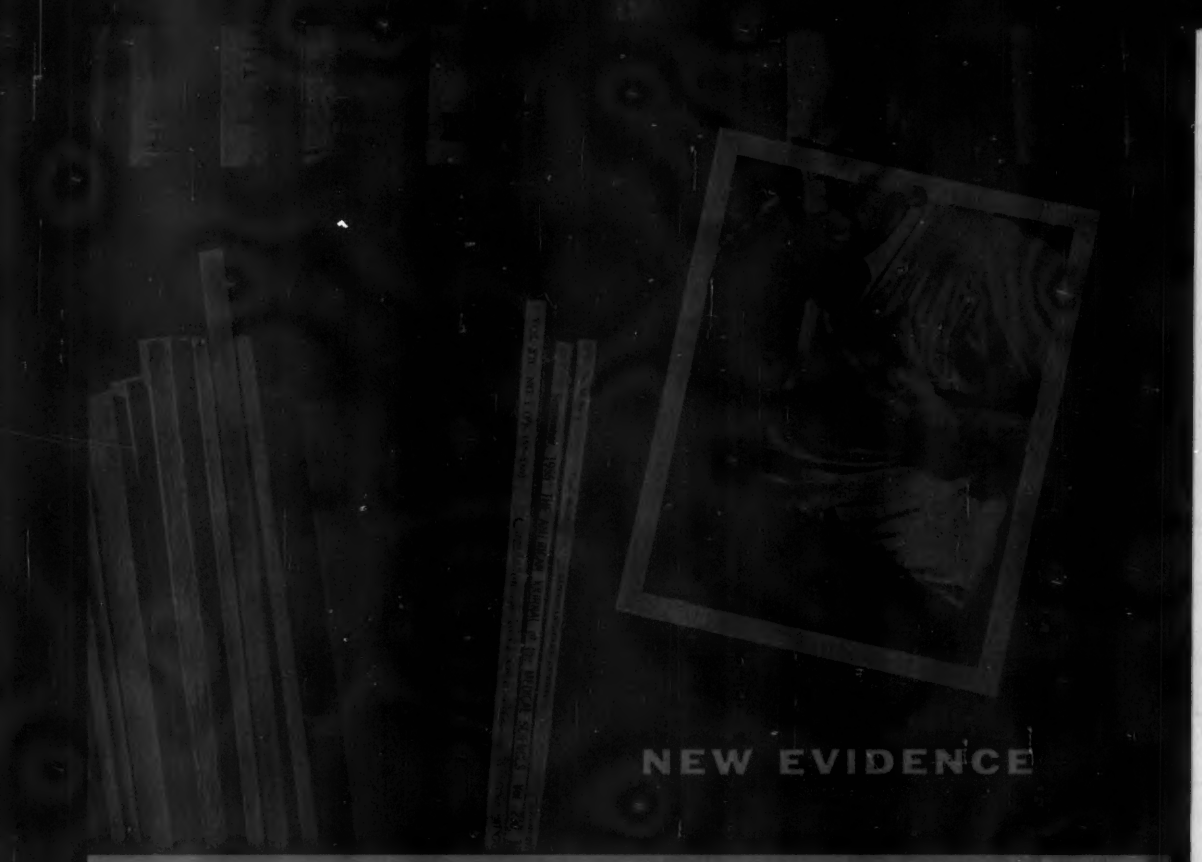

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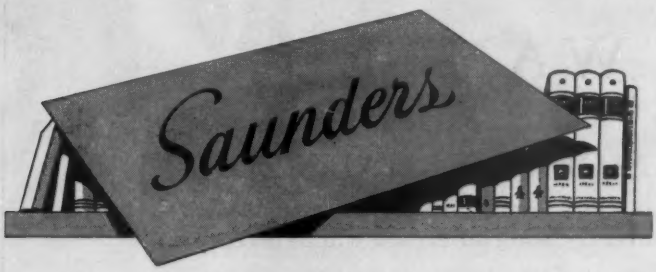

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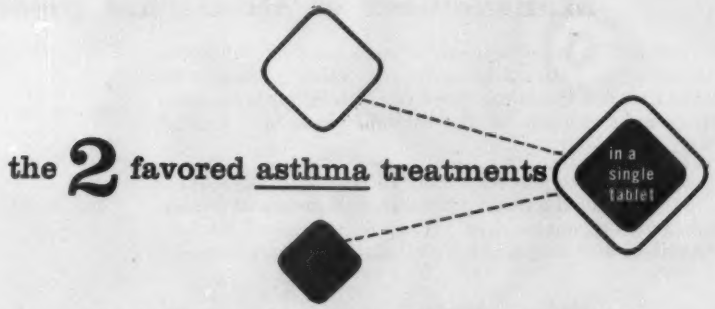

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References:

1. Winsor, T.: Am. J. M. Sc. *230*:133 (Aug.) 1955. 2. Grimson, K. S.: J.A.M.A. *158*:359 (June 4) 1955. 3. Grimson, K. S., Tarazi, A. K., and Frazer, J. W., Jr.: Circulation *11*:733 (May) 1955. 4. Grimson, K. S., Tarazi, A. K., and Frazer, J. W., Jr.: Angiology *6*:507 (Dec.) 1955. 5. Strawn, J. R., and Moyer, J. H.: Personal communication, 1955. 6. Maxwell, R. D. H., and Howie, T. J. G.: Brit. M. J. *2*:1189 (Nov. 12) 1955.

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3	50 mg.	25 mg.
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44	50 mg. daily	35 responded well; 14 of these became normotensive. All patients received reserpine as base therapy.	**	5
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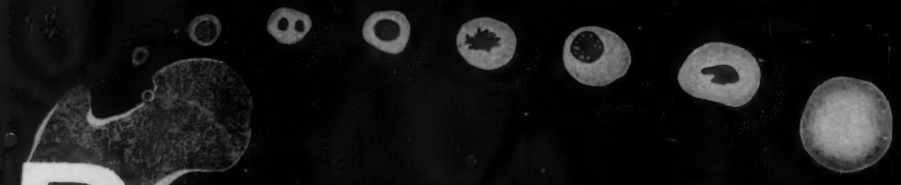

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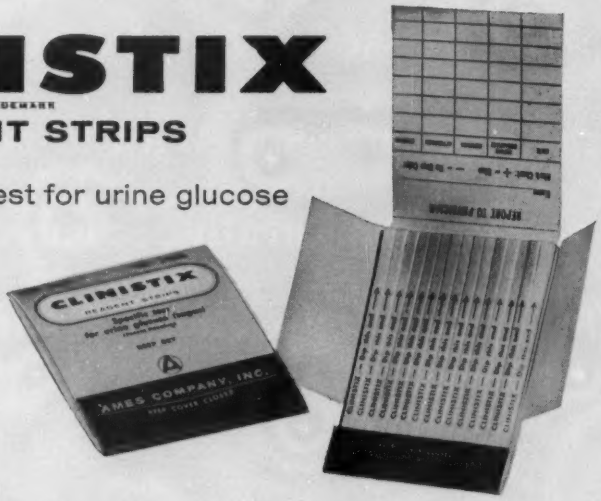

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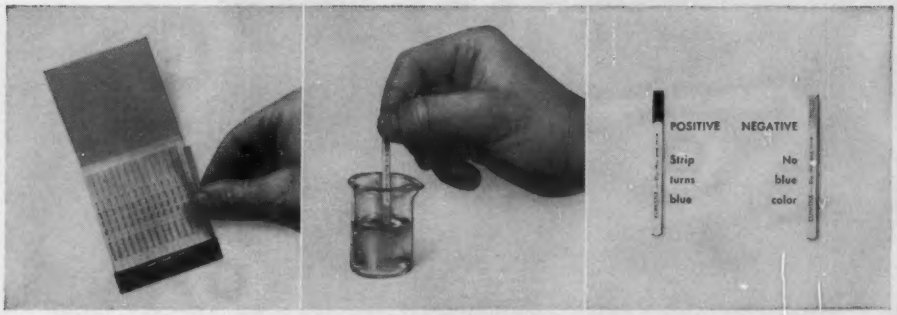

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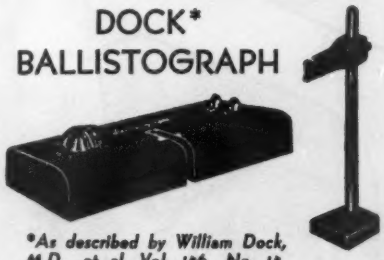

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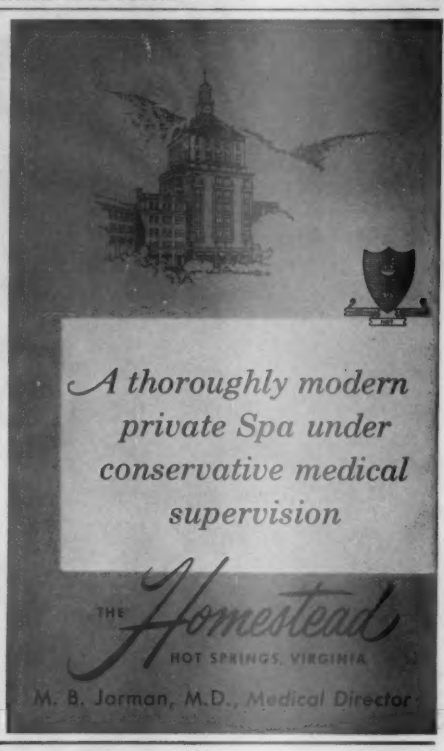
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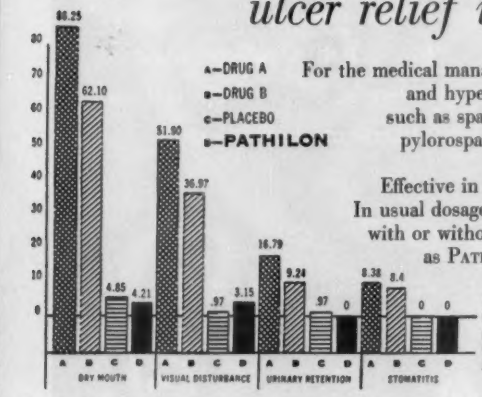

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2. J.A.M.A. 160:389 (Feb. 4) 1956.

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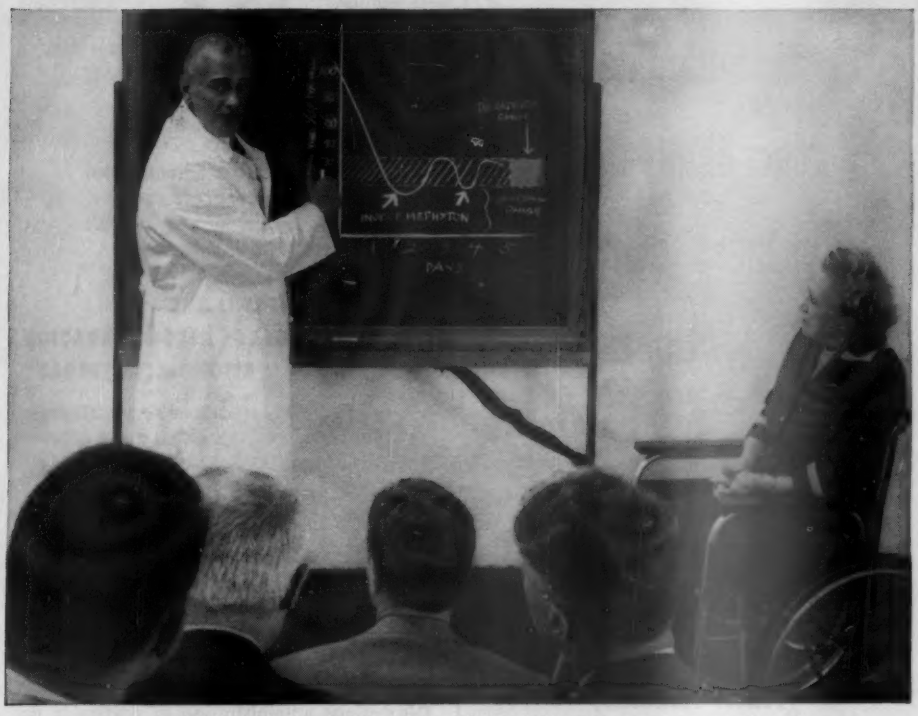

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"It is shown that oil-soluble vitamin K_1 is more effective than any other agent now available in combating drug-induced hypoprothrombinemia."[1] However, the usefulness of Mephyton lies not only in overcoming bleeding emergencies, but also in adjusting upwards to safe therapeutic levels unduly prolonged prothrombin times. Mephyton permits the clinician to do this easily and without gross changes in the regular anticoagulant dosage. . . ."no untoward effects have been observed to follow the administration of vitamin K_1."[1]

INDICATIONS: Hypoprothrombinemia due to Dicumarol®, Cumopyran®, Tromexan®, Hedulin®, 'Dipaxin', warfarin and other phenylindanediones; also when due to antibiotics, salicylates, obstructive jaundice, hepatic disease, and impaired gastrointestinal absorption.

SUPPLIED: In boxes of six 1-cc. ampuls, 50 mg. of vitamin K_1 per cc.

1. Gamble, J. R., *et al.*, *Arch. Int. Med.* 95:52, January 1955.

SHARP & DOHME

Philadelphia 1, Pa.
DIVISION OF MERCK & CO., INC.

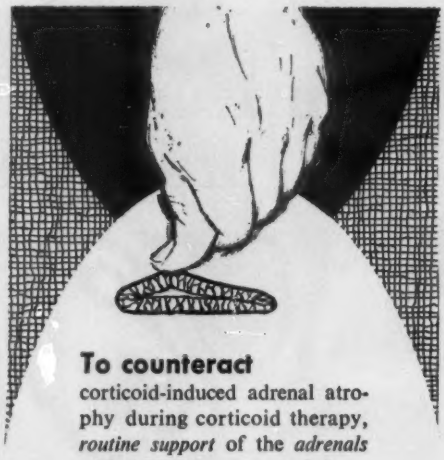
single
sulfonamide
specifically for
urinary tract
infections

direct/effective

"THIOSULFIL"®
Brand of sulfamethizole

greater solubility
means rapid
action with
minimum side effects

AYERST LABORATORIES
New York, N. Y. • Montreal, Canada
5652



To counteract
corticoid-induced adrenal atrophy during corticoid therapy, *routine support* of the *adrenals with ACTH is recommended.*

THIS IS THE
PROTECTIVE DOSAGE RECOMMENDATION
FOR COMBINED CORTICOID-ACTH THERAPY

- When using *prednisone* or *prednisolone:* for every 100 mg. given, inject approximately 100 to 120 units of HP* ACTHAR *Gel.*
- When using *hydrocortisone:* for every 200 to 300 mg. given, inject approximately 100 units of HP* ACTHAR *Gel.*
- When using *cortisone:* for every 400 mg. given, inject approximately 100 units of HP*ACTHAR *Gel.*

Discontinue administration of corticoids on the day of the HP*ACTHAR *Gel* injection.

HP*ACTHAR® *Gel*
(IN GELATIN)
The Armour Laboratories brand of purified adrenocorticotropic hormone—corticotropin (ACTH)

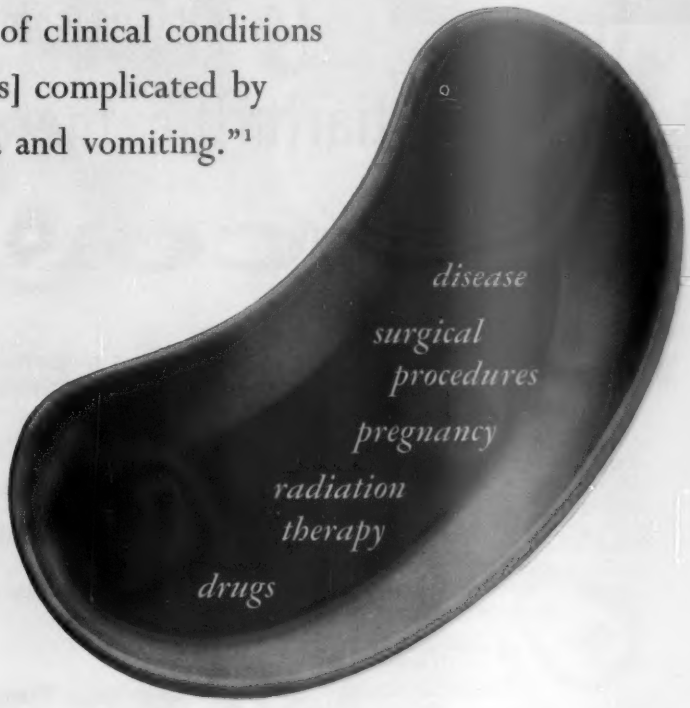
*Highly Purified

Unsurpassed in Safety and Efficacy
More than 42,000,000 doses of ACTH have been given

THE ARMOUR LABORATORIES
A DIVISION OF ARMOUR AND COMPANY
KANKAKEE ILLINOIS

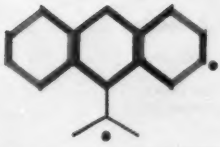
THORAZINE*

"An effective antiemetic agent for a wide range of clinical conditions [and situations] complicated by nausea and vomiting."[1]



1. Moyer, J.H., et al.: Arch. Int. Med. 95:202 (Feb.) 1955.

'Thorazine' is available in ampuls, tablets and syrup (as the hydrochloride), and in suppositories (as the base).



Smith, Kline & French Laboratories, Philadelphia

*T.M. Reg. U.S. Pat. Off. for chlorpromazine, S.K.F.

a "judicious combination..."

for antiarthritic therapy

SALCORT*

That cortisone and the salicylates have a complementary action has been well established.[1-5] In rheumatic conditions, functional improvement and a sense of feeling well are noted early. No withdrawal reactions have been reported.

One clinician states: "By a judicious combination of the two agents . . . it has been possible to bring about a much more favorable reaction in arthritis than with either alone. Salicylate potentiates the greatly reduced amount of cortisone present so that its full effect is brought out without evoking undesirable side reactions."[1]

INDICATIONS:

Rheumatoid arthritis . . . Rheumatoid spondylitis . . . Rheumatic fever . . . Bursitis . . . Still's disease . . . Neuromuscular affections

EACH TABLET CONTAINS:

Cortisone acetate	2.5 mg.
Sodium salicylate	0.3 Gm.
Aluminum hydroxide gel, dried .	0.12 Gm.
Calcium ascorbate	60 mg.
(equivalent to 50 mg. ascorbic acid)	
Calcium carbonate	60 mg.

* U.S. Pat. 2,691,662

1. Busse, E.A.: Treatment of Rheumatoid Arthritis by a Combination of Cortisone and Salicylates. Clinical Med. 11:1105 (Nov., 1955).
2. Roskam, J., VanCawenberge, H.: Abst. in J.A.M.A., 151:248 (1953).
3. Coventry, M.D.: Proc. Staff Meet., Mayo Clinic, 29:60 (1954).
4. Holt, K.S., et al.: Lancet, 2:1144 (1954).
5. Spies, T.D., et al.: J.A.M.A., 159:645 (Oct. 15, 1955).

BRISTOL, TENNESSEE
NEW YORK
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The S. E. Massengill company

The preferred hematinic with PEPTONIZED iron

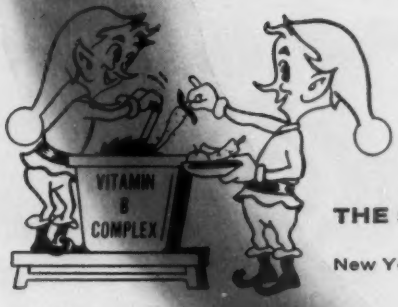
LIVITAMIN®

Peptonized iron is virtually predigested—better absorbed, better utilized and less toxic than ferrous sulfate. Anemias refractory to other forms of iron will often respond promptly to Livitamin therapy.

The Livitamin formula, containing the B complex, provides integrated therapy to correct the blood picture, and to improve appetite and digestion.

Each fluidounce contains:

Iron peptonized (Equiv. in elemental iron to 71 mg.)	420 mg.
Manganese citrate, soluble	158 mg.
Thiamine hydrochloride	10 mg.
Riboflavin	10 mg.
Vitamin B_{12} (crystalline)	20 mcg.
Niacinamide	50 mg.
Pyridoxine hydrochloride	1 mg.
Pantothenic acid	5 mg.
Liver fraction 1	2 Gm.
Rice bran extract	1 Gm.
Inositol	30 mg.
Choline	60 mg.



THE S. E. MASSENGILL COMPANY

Bristol, Tennessee

New York Kansas City San Francisco

air...without adding an extra mm./Hg.

This case is another example of the life-saving potential of BRONKEPHRINE. No longer is it necessary to expose your asthmatics (even if hypertensive) to the risk of heightened blood pressure. An effective bronchodilator without pressor side effects—BRONKEPHRINE—is at hand.

Distinguished authors consistently reveal that the much-sought-after bronchodilator without significant side reactions has been found with the discovery of BRONKEPHRINE.

BRONKEPHRINE's lack of pressor effect[1,2-5] is of "...major importance in treating patients in whom hypertension or cardiac disease is a problem,"[1] or, for that matter, in treating *any* asthma patient. Along with this welcome fact, add the advantage of BRONKEPHRINE's lack of excitation[1,2,6]—a level of CNS stimulation far lower than that of epinephrine.[6]

One clinician found this property of BRONKEPHRINE to be of benefit "...particularly in the control of asthma in children."[1]

But what about BRONKEPHRINE in long-term therapy? One reason why BRONKEPHRINE has been called a "superior tool for the treatment of bronchial asthma"[1] has been its relative lack of tolerance, a clear advantage in long-term management. So why not use BRONKEPHRINE as your bronchodilator of choice in *any* asthma? It tends to develop tolerance "...far less frequently and to a lesser degree than epinephrine."[1]

Bronkephrine®

(ETHYLNOREPINEPHRINE BREON)

is available in 10 cc. multidose vials containing 2 mg. BRONKEPHRINE per cc.

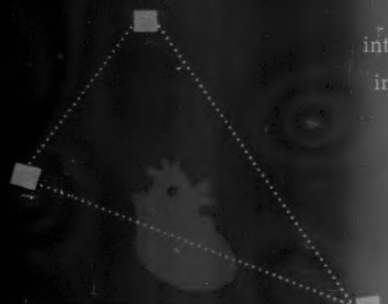
Write to this address for more information, or a clinical sample, for your practice.

George A. Breon & Company
1450 Broadway, New York 18, N. Y.

1. Foland, J. P.: Postgrad. Med. 18:397, 1955.
2. Bubert, H. M., and Doenges, J. P.: Bull. School Med. Univ. Maryland 31 (No. 1), 1946.
3. Tainter, M. L.; Pedden, J. R., and James, M.: J. Pharmacol. & Exper. Therap. 51:371, 1934.
4. Pedden, J. R.; Tainter, M. L., and Cameron, W. M.: J. Pharmacol. & Exper. Therap. 55:242, 1935.
5. Hartman, M. M.: Ann. Allergy 3:366, 1945.
6. Schulte, J. W.; Reif, E. C.; Bacher, J. A.; Lawrence, W. S., and Tainter, M. L.: J. Pharmacol. & Exper. Therap. 71:62, 1941.

Breon

V. L., age 56. Status asthmaticus. Under oxygen, B.P. 134/92. BRONKEPHRINE intravenously—"dramatic" result, "...no rise in blood pressure or any other side reaction."[1] Oxygen not needed again.



most convenient
digitalis
preparation...
change route
any time
without changing
dose or interval

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Now with Digitaline Nativelle Intramuscular, a complete range of routes of administration is available. This preparation—specifically designed for I.M. use—avoids irritation often encountered when I.V. forms are administered intramuscularly. The dosage schedule with DIGITALINE NATIVELLE need never be changed because of change in the route of administration. The same advantages are provided by all forms, enabling the physician to cope with any change in the patient's status. Prescribe DIGITALINE NATIVELLE—the original pure crystalline digitoxin • pure active principle • complete absorption • rapid onset of action • smooth, even maintenance • frequent dosage readjustment unnecessary • virtual freedom from gastric upset

Consult your Physicians' Desk Reference for dosage information.

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Full Diuretic Control with Fewer Injections

The THIOMERIN program combines parenteral and suppository therapy to solve a major diuretic problem—drastic diuresis, patient alternately dry and waterlogged.

Parenteral THIOMERIN initiates diuresis . . . supplemented by THIOMERIN Suppositories to permit maximal spread between injections, to prevent fluid accumulation, and to maintain dry weight. Together, they offer a well-tolerated and convenient regimen for smooth edema control.[1]

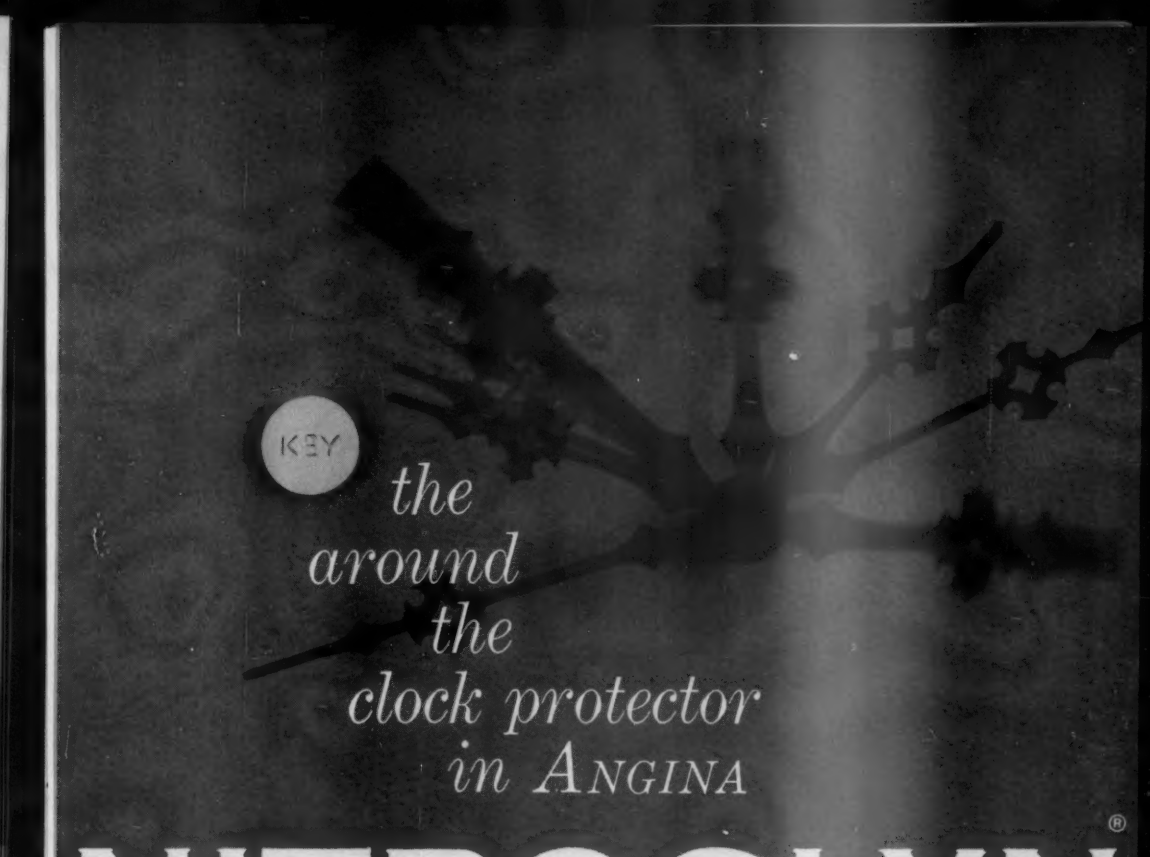
Supplied: THIOMERIN Suppositories, boxes of 12. Injection THIOMERIN Solution, vials of 2 cc., boxes of 12; vials of 10 cc. Injection THIOMERIN (lyophilized), vials of 1.4 Gm. (10 cc. upon reconstitution) and 4.2 Gm. (30 cc. upon reconstitution).

1. Daly, J.W.: Am. J. M. Sc. *228*:440 (Oct.) 1954.

INJECTION RECTAL SUPPOSITORIES

THIOMERIN® Sodium

MERCAPTOMERIN SODIUM



the around the clock protector in ANGINA

NITROGLYN®

(SUSTAINED ACTION NITROGLYCERIN)

..."Has been proven effective in the treatment and prevention of angina pectoris attacks.... The effect... sets in very quickly and lasts for a very long time..."[1]

..."In summary, the agent seems to be quite effective and seems to be devoid of harmful side effects even when continued over long periods of time..."[2]

..."A highly useful preparation of slow release nitroglycerin..."[3]

..."Results in alleviation of the angina in a significantly high percentage of cases."[4]

***NITROGLYN** tablets are available in two dosage forms, gr. 1/25th and gr. 1/10th.*

Literature and samples available on request.

KEY CORPORATION
MIAMI 37, FLORIDA

References:

1. **HUEBER, E. F., M.D.;** *et al.*, *Wiener Klinische Wochenschrift, Vienna, Austria; May, 1955 (1st University Medical Clinic)*
2. **BOYD, L. J., M.D.,** *Director of Medicine, New York Medical College; Flower & Fifth Avenue Hospital, N. Y. C.; personal communication*
3. **PLOTZ, MILTON, M.D., N.Y.C.;** *personal communication*
4. **EICHERT, HERBERT, M.D.;** *Chief Cardiology Section, Jackson Memorial Hospital, Miami, Fla., personal communication*

Lift the depressed patient up to normal without fear of overstimulation . . .

with new

Ritalin®

A HAPPY MEDIUM IN PSYCHOMOTOR STIMULATION

• *Boosts the spirits, relieves physical fatigue and mental depression . . . yet has no appreciable effect on blood pressure, pulse rate or appetite.*

Ritalin is a mild, safer central-nervous-system stimulant which gently improves mood, relieves psychogenic fatigue "without let-down or jitters . . ."[1] and counteracts oversedation caused by barbiturates, chlorpromazine, rauwolfia, and antihistamines.

Ritalin is "a more effective and less over-reactive drug than amphetamine or its derivatives."[2] It does not produce the "palpitation, nervousness, jitteriness, or undue pressure in the chest area . . . so frequently mentioned by patients on [dextro-amphetamine sulfate]."[3]

Dosage: 5 to 20 mg. b.i.d. or t.i.d., adjusted to the individual.

RITALIN® hydrochloride (methyl-phenidylacetate hydrochloride CIBA)

References: 1. Pocock, D. G.: Personal communication. 2. Harding, C. W.: Personal communication. 3. Hollander, W. M.: Personal communication.

Supplied: Tablets, 5 mg. (yellow) and 10 mg. (blue); bottles of 100, 500 and 1000. Tablets, 20 mg. (peach-colored); bottles of 100 and 1000.

a/21934

CIBA
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looked over often...

the patient with nonspecific rheumatism

NOW—thoroughgoing relief with

NEW SIGMAGEN

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Prednisone	0.75 mg.	—best of the new
Acetylsalicylic acid . . .	325 mg.	—best of the old
Ascorbic acid	20 mg.	
Aluminum hydroxide . .	75 mg.	

antirheumatic • anti-inflammatory • analgesic • supportive

Combined effectiveness of the antirheumatic agents in SIGMAGEN permits maintenance of clinical relief at minimal dosages.

SIGMAGEN,® brand of corticoid-analgesic compound.
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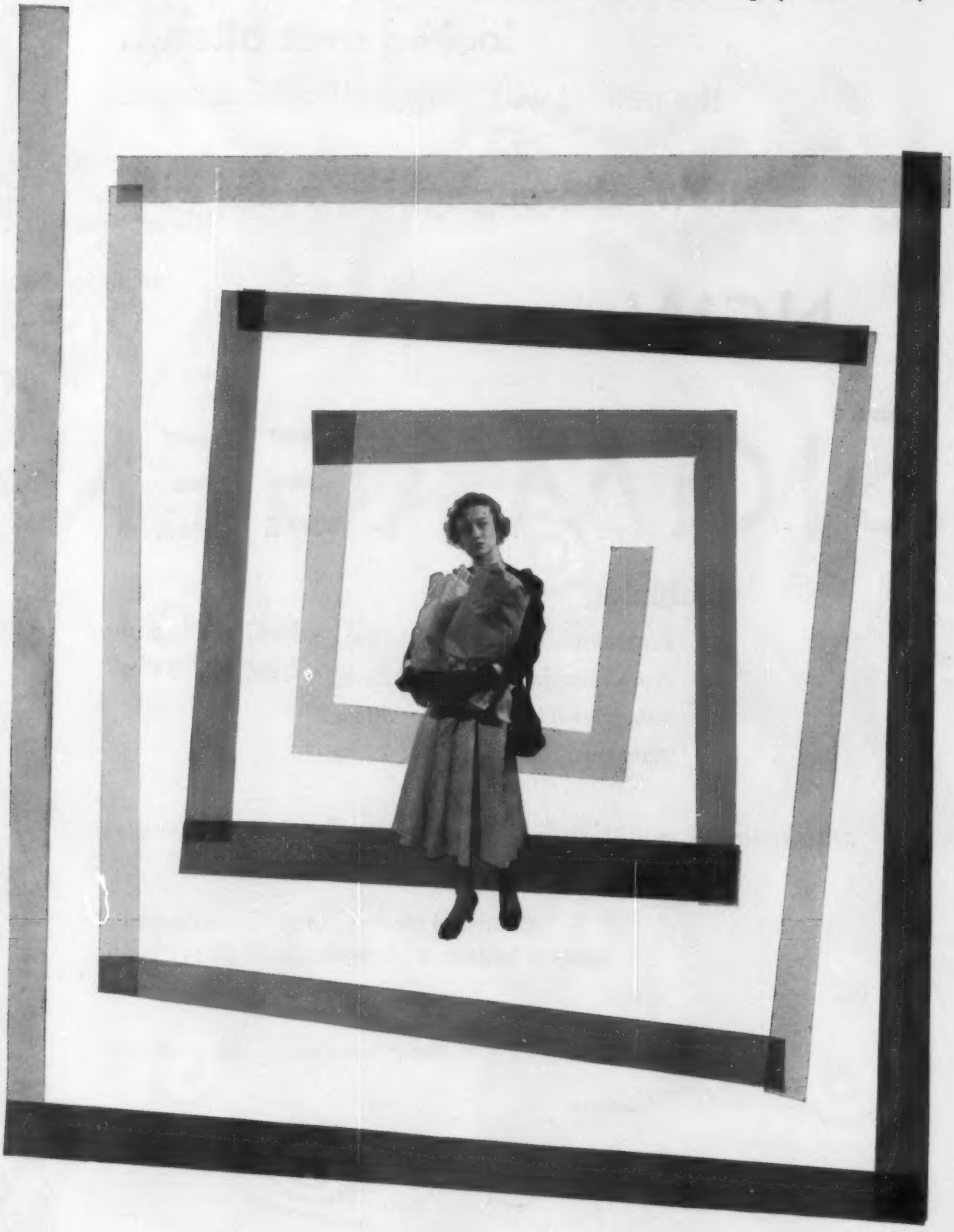
surrounded by a monotonous routine of daily problems,



disappointments and responsibilities . . .

to help the depressed and anxiety-ridden housewife who is surrounded by a monotonous routine of daily problems, disappointments and responsibilities . . .

With 'Dexamyl' you can often help her to face her problems; help her to regain lost interests; help her to rediscover the zest and purpose in life. The normalizing effect of 'Dexamyl' is free of the dullness caused by many "anti-anxiety" agents alone; free of the excitation sometimes caused by stimulants alone. Her mood normalized, the disturbing mental and physical symptoms often vanish.

DEXAMYL* tablets • elixir • Spansule† capsules

smoothly and subtly relieves both anxiety and depression

Each 'Dexamyl' Tablet or teaspoonful (5 cc.) of the Elixir contains Dexedrine* (dextro-amphetamine sulfate, S.K.F.), 5 mg., and amobarbital, ½ gr.

Each 'Dexamyl' *Spansule* No. 1 gradually releases the equivalent of *two* tablets; each 'Dexamyl' *Spansule* No. 2—the *standard* strength—gradually releases the equivalent of *three* tablets.

Smith, Kline & French Laboratories, Philadelphia

*T.M. Reg. U.S. Pat. Off.
†T.M. Reg. U.S. Pat. Off. for sustained release capsules, S.K.F.
Patent Applied For.

FOR CONTINUOUS VISUAL MONITORING OF PHYSIOLOGICAL EVENTS

MODEL 169A

SANBORN VISO-SCOPE

DESIGNED for compatibility with other SANBORN equipment (examples, right), simplified operation via minimum controls (illustration, above), and *precise* control of the base line sweep, the Model 169A Viso-Scope now permits the owner or purchaser of SANBORN recording instruments to greatly widen their field of usefulness.

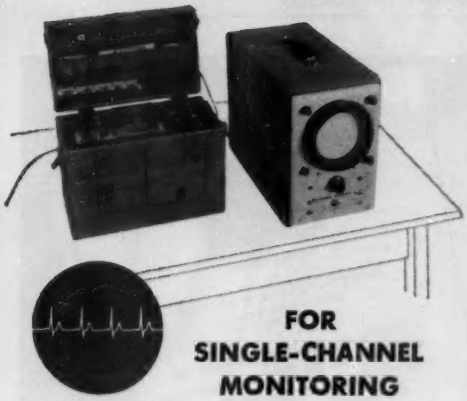
The cathode ray tube selected for this 'scope has a *dual coating* which produces a beam image of exceptional sharpness and long persistence on the orange screen-filter (when monitoring) and of extreme brightness and short duration on the blue screen-filter (for photography). When photography is desired, a Fairchild or DuMont oscilloscope camera may be mounted on the screen bezel (or any common camera may be used).

Sweep speeds of 25, 50 and 100 millimeters per second are obtainable instantaneously, and enlargement on the Viso-Scope screen of a segment of the tracing which is of particular interest may be made at any time.

Typical applications of the Viso-Scope include: observation of changes in the electrocardiogram resulting from use of drugs; pressure monitoring in catheterization during manipulation of the catheter; and a more precise study of complex wave forms by an instantaneous increasing of the sweep speed, such as in myography, phonocardiography, and small animal electrocardiography.

Descriptive literature on the Viso-Scope complete with diagrams showing hook-up requirements of various Sanborn recorders is available on request.

The Model 169A-OR (Operating Room) Viso-Scope is a completely self-contained oscilloscope-amplifier unit, specially designed for visual ECG presentation during surgery in the presence of explosive gases. Viewing unit is supported at or above five foot height on a steel column, and may be turned and tilted for best viewing angle. Provision is made for connection to a remote ECG, when written records are also desired. May also be used for display of sphygmograms, pneumograms, etc.



FOR SINGLE-CHANNEL MONITORING

Electrocardiograms may be continuously monitored with a Viso-Scope connected directly to a Sanborn Viso-Cardiette (Model 572 or 51). Or, a Model 128 or 141 Sanborn Recorder may be similarly used for viewing other phenomena such as pressure, temperature, sphygmograms, pneumograms, myograms, etc., with suitable transducers employed.

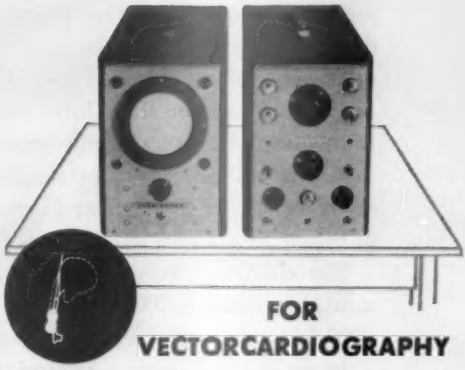
Written records may be made whenever desired during the monitoring. Selection of sweep speeds on the Viso-Scope (see left page) is particularly advantageous to owners of these instruments.

FOR MONITORING UP TO FOUR EVENTS SIMULTANEOUSLY

The Sanborn Electronic Switch, shown above connected to each channel of a Model 154M four-channel Poly-Viso, is designed for use with any Sanborn two- or four-channel *direct writing* recording system. It permits *simultaneous* observation of as many phenomena as the system is set up to record, and Viso-Scope thus connected appears to be operating with *separate beams*. Controls permit liberal relative positioning of beams on the scope screen, and *individual* sensitivity control. These adjustments have no effect on the recording instrument.

HIGHER SPEED MONITORING

With the addition of an attachable booster amplifier the Viso-Scope may be used with a Sanborn Twin-Beam Cardiette, to display phenomena of higher frequency such as are encountered in phonocardiography, small animal electrocardiography, high fidelity human electrocardiography, etc. Separate oscilloscope jacks on the Twin-Beam permit ready selection of the signal from either "phono" or ECG channel, for alternate display on the Viso-Scope screen.

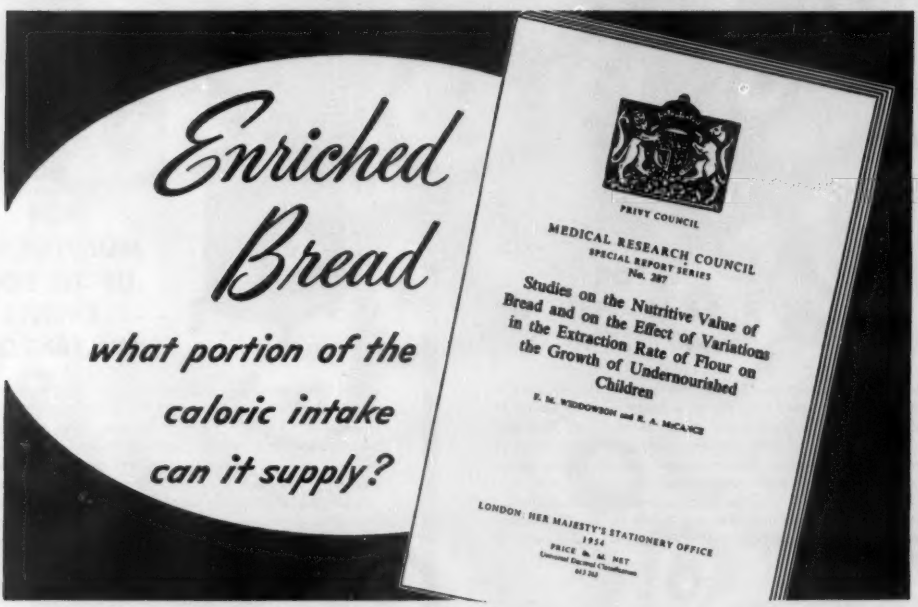


FOR VECTORCARDIOGRAPHY

The Sanborn Model 185 Vector System (or vector amplifier) shown above right, has been specifically designed for use with the Viso-Scope, for displaying either vector loops or ECG complexes. This instrument's lead selector switch, together with a specially-marked 9-wire patient cable and extra electrodes, permit the instantaneous selection of either cube or tetrahedral vector leads, or ECG leads, for Viso-Scope display. Adequate sensitivity (10" per mv) provides clear showing of P and T loops, as well as QRS. Additionally (via installation of timing transformer in the Viso-Scope) the Vector system provides Z axis, or intensity modulation for indication of speed and direction of sweep trace.

SANBORN COMPANY

CAMBRIDGE 39, MASSACHUSETTS


Enriched
Bread
what portion of the
caloric intake
can it supply?
PRIVY COUNCIL
MEDICAL RESEARCH COUNCIL
SPECIAL REPORT SERIES
No. 287
Studies on the Nutritive Value of Bread and on the Effect of Variations in the Extraction Rate of Flour on the Growth of Undernourished Children
LONDON: HER MAJESTY'S STATIONERY OFFICE
1954

A striking observation was made in a recently reported nutrition study. Undernourished children in a German orphanage, placed on diets providing a high percentage of their total calories in the form of bread, not only improved in health, but "in spite of the simple diet provided" gained in weight and increased in height at a highly satisfactory rate.*

The children received daily supplements of vitamin A, 2000 I.U., vitamin D, 1000 I.U., and ascorbic acid, 25 mg.

In the words of the investigators: "One of the most striking findings, . . . and perhaps the most unexpected one, was the remarkable way in which the general condition of all the children . . . improved . . ."

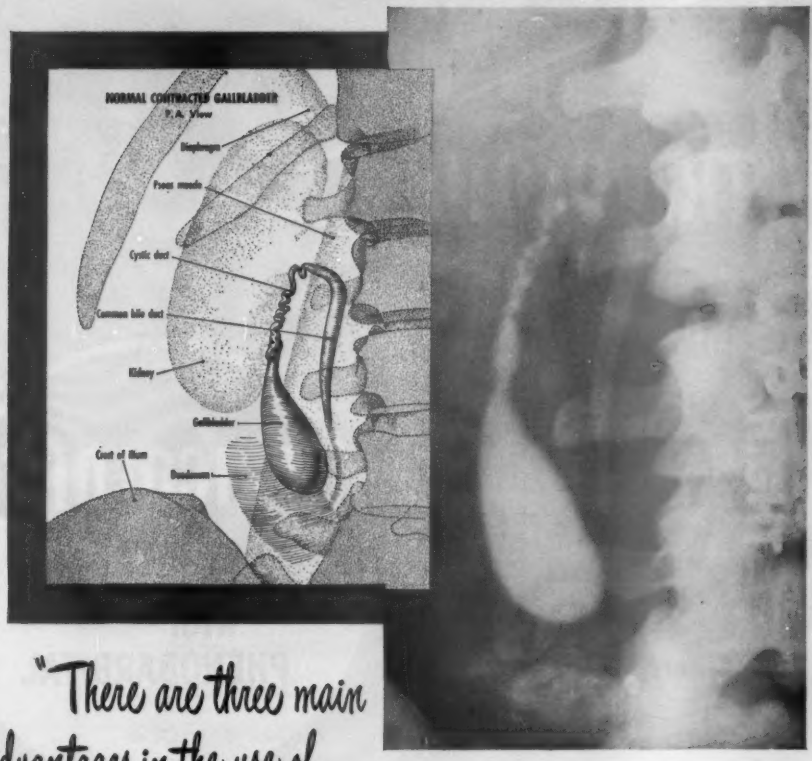
"Probably the most important finding concerns the high nutritive value of wheat in any of the forms customarily consumed by man. . . . [The diets fed] provided undernourished children aged 5-15 years with all the nutrients required for a high rate of growth and development for a period of 18 months."

Enriched bread, made from 70 per cent extraction flour and very similar to enriched bread sold in the United States, was among the breads used. While the diets used in this study are not justified in this country with its abundant food supply, hence do not merit consideration for applicability here, they nevertheless serve to emphasize again the high nutritional value of enriched bread.

*Widdowson, E. M., and McCance, R. A.: Studies on the Nutritive Value of Bread and on the Effect of Variations in the Extraction Rate of Flour on the Growth of Undernourished Children, Medical Research Council, Special Report Series, No. 287, London, Her Majesty's Stationery Office, 1954.

The nutritional statements made in this advertisement have been reviewed by the Council on Foods and Nutrition of the American Medical Association and found consistent with current authoritative medical opinion.

AMERICAN BAKERS ASSOCIATION 20 North Wacker Drive • Chicago 6, Illinois



"There are three main advantages in the use of

Telepaque®

SUPERIOR ORAL CHOLECYSTOGRAPHY AND CHOLANGIOGRAPHY

1. **Excellent cholecystograms are readily obtainable.**
2. **The side reactions are usually minimal, only rarely very disturbing, and often completely absent.**
3. **In a fairly large percentage of cases, the cystic and the common ducts are quite definitely outlined, and occasionally even the hepatic duct."**

Buckstein, Jacob: The Digestive Tract in Roentgenology. Philadelphia, J. B. Lippincott Co., 2nd ed., 1953, vol. 2, p. 1003.

DOSAGE:

The average adult dose of Telepaque is 3 Gm. (6 tablets). In persons of thin or medium build, weighing less than 150 lb., 2 Gm. (4 tablets) may be sufficient.

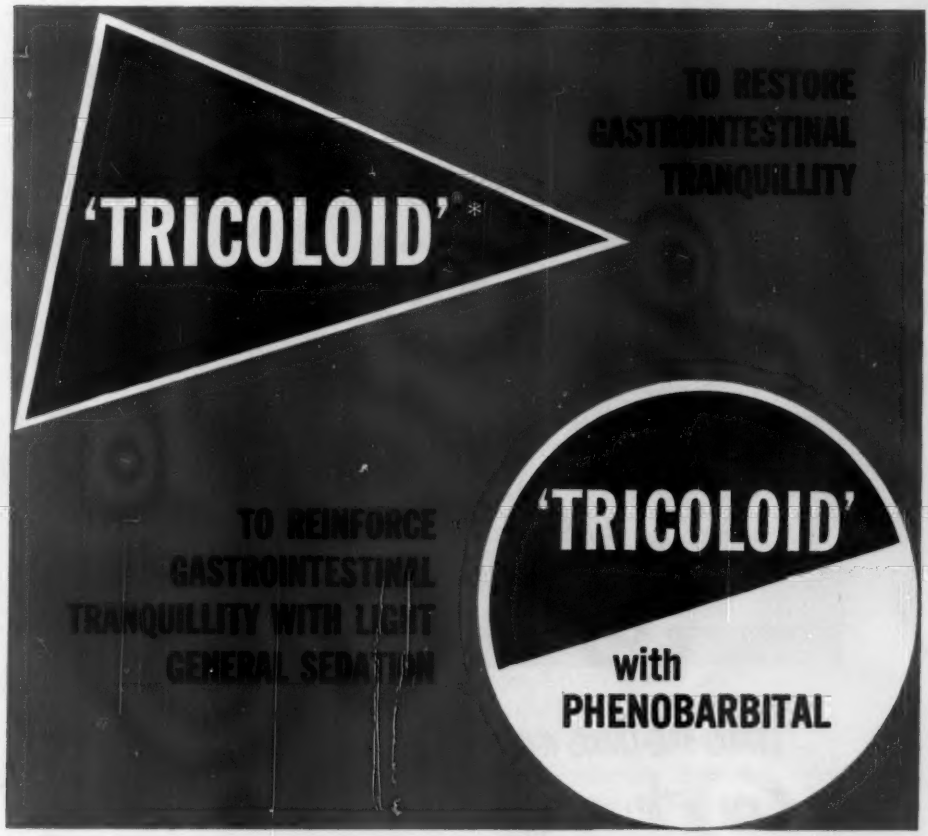
SUPPLIED:

Tablets of 0.5 Gm. in envelopes of 6 tablets, boxes of 5 and 25 envelopes, and bottles of 500.

Winthrop LABORATORIES

NEW YORK 18, N. Y. WINDSOR, ONT.

Telepaque (brand of iopanoic acid), trademark reg. U. S. Pat. Off.



'TRICOLOID' or **'TRICOLOID' with Phenobarbital** is indicated, according to the degree of emotional tension which accompanies the symptoms, for the medical management of:

"lower bowel syndrome,"
nervous indigestion,
functional gastroenteritis,
peptic ulcer

**'TRICOLOID' brand Tricyclamol 50 mg. Sugar-coated tablets*
'TRICOLOID' brand Tricyclamol 50 mg. with Phenobarbital 16 mg. (gr. ¼) Sugar-coated tablets

Both products in bottles of 100 and 1,000

BURROUGHS WELLCOME & CO. (U.S.A.) INC., *Tuckahoe, New York*

new -

Against Pathogen & Pain

in urinary tract infections

Azo Gantrisin combines the single, soluble sulfonamide, Gantrisin, with a time-tested urinary analgesic - in a single tablet.

Prompt relief of pain and other discomfort is provided together with the wide-spectrum antibacterial effectiveness of Gantrisin which achieves both high urinary and plasma levels so important in both ascending and descending urinary tract infections.

Each Azo Gantrisin tablet contains 0.5 Gm Gantrisin 'Roche' plus 50 mg phenylazo-diamino-pyridine HCl. Gantrisin® - brand of sulfisoxazole

ROCHE | Original Research in Medicine and Chemistry

For patients pursued by their own emotions —

Noludar 'Roche' will help solve the problem. Not a barbiturate, not habit forming, 50 mg t.i.d. provides daytime sedation without somnolence, while 200 mg h.s. induces a sound night's sleep without hangover.
Noludar tablets, 50 and 200 mg; elixir, 50 mg per teaspoon.
Hoffmann - La Roche Inc.
Nutley 10, New Jersey

Noludar®
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for control of fluid balance

By inhibiting carbonic anhydrase, DIAMOX produces prompt, ample diuresis. Taken in the morning, its effect ceases within 6-12 hours thereby permitting uninterrupted sleep at night.

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Acetazolamide Lederle

the nonmercurial diuretic

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1. Balfour, D. C., Jr.: Am. J. Gastroenterol. 22:181, 1954. 2. Burke, J. O., et al.: Internat. Rec. Med. & Gen. Practice Clin. 167:627, 1954. 3. Sternberg, S. D., and Greenblatt, I. J.: Ann. Allergy 9:196, 1951.

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1. Cass, L. J. and Frederik, W. S.: Malt Soup Extract as a Bowel Content Modifier in Geriatric Constipation. Journal-Lancet, 73:414 (Oct.) 1953.

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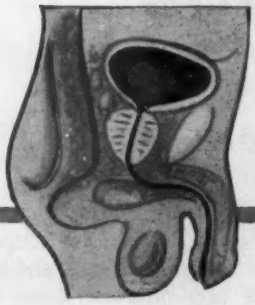

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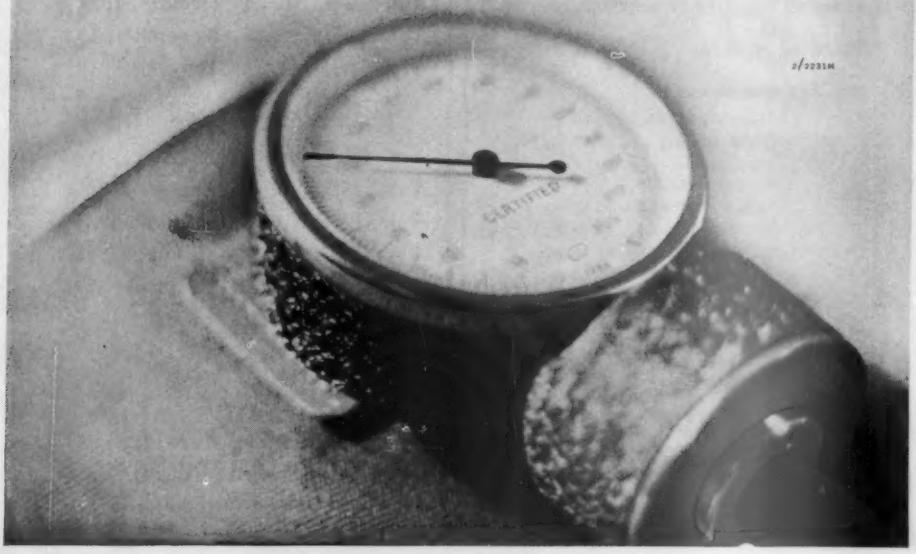

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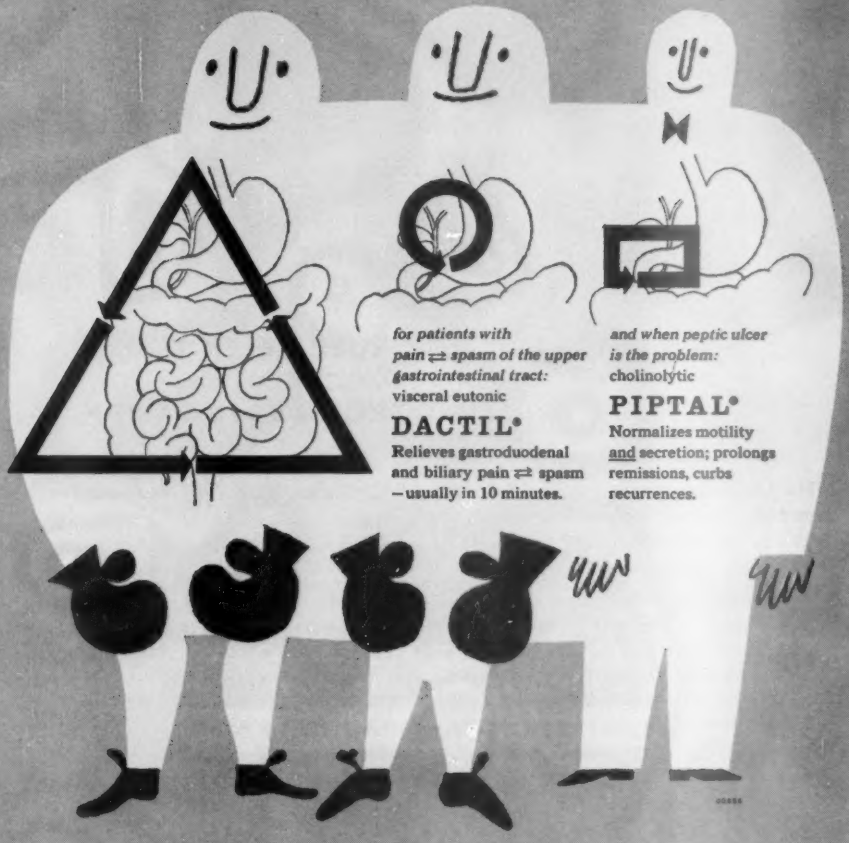

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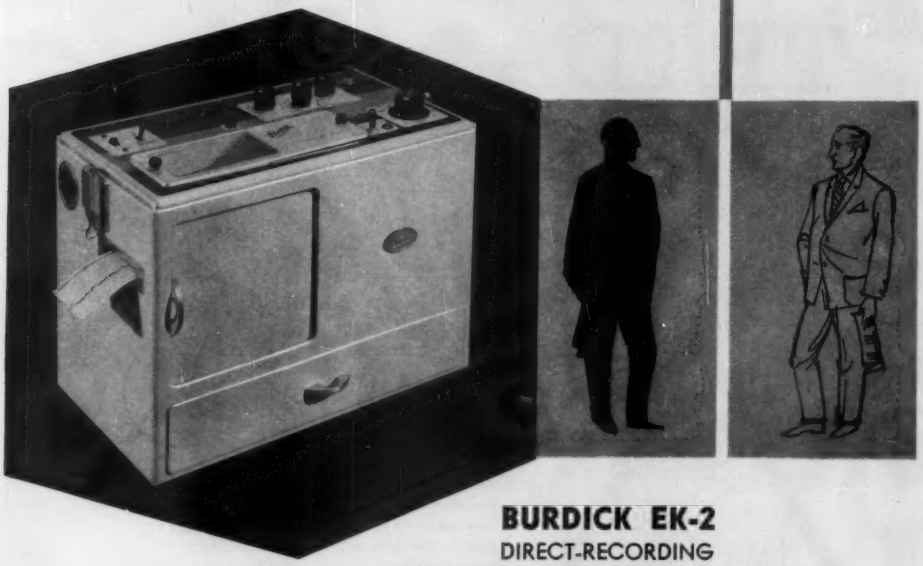

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References: 1. Ehrlich, J. C.: Arizona Med. *12:* 239 (June) 1955. 2. Weiss, A., and Steigmann, F.: Am. J. M. Sc. *227:* 188 (Feb.) 1954. 3. Dimitroff, S. P.; Griffith, G. C.; Thorner, M. C., and Walker, J.: Ann. Int. Med. *39:* 1189 (Dec.) 1953. 4. Hejtmancik, M. R., and Herrmann, G. R.: Texas St. J. M. *51:* 238 (May) 1955. 5. Batterman, R. C.; DeGraff, A. C., and Rose, O. A.: Circulation *5:* 201 (Feb.) 1952. 6. Denham, R. M.: J. Kentucky St. M. Assoc. *53:* 209 (Mar.) 1955.

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1. Denko, C. W.; Ruml, D., and Bergenstal, D. M.: Am. Pract. & Digest Treat. 6:1865, 1955.
2. Holbrook, W. P.: M. Clin. North America 39:405, 1955.
BUTAZOLIDIN® (phenylbutazone GEIGY). Red coated tablets of 100 mg.

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for direct, topical management of

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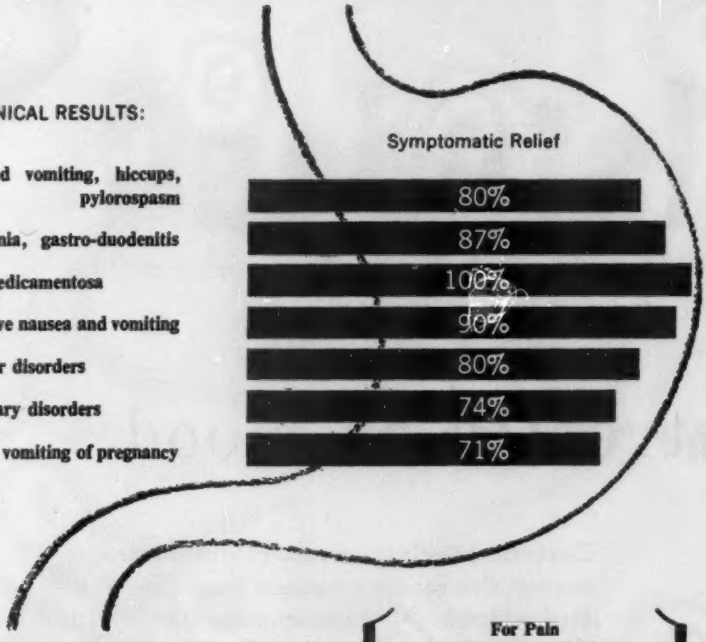

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Pabirin circumvents the potential hazards of steroid therapy, such as adrenal atrophy, while being equally effective. It contains neither sodium nor potassium, an advantage when either of these electrolytes must be restricted.

Bibliography:
Joint Committee of the Medical Research Council and Nuffield Foundation: Brit. M. J. *2*:695 (Sept. 17) 1955.
Editorial: Brit. M. J. *2*:725 (Sept. 17) 1955.
Lowman, E. W., and others: GP *12*:69 (Nov.) 1955.

Each capsule contains:

Acetylsalicylic acid	(5 gr.) 300 mg.
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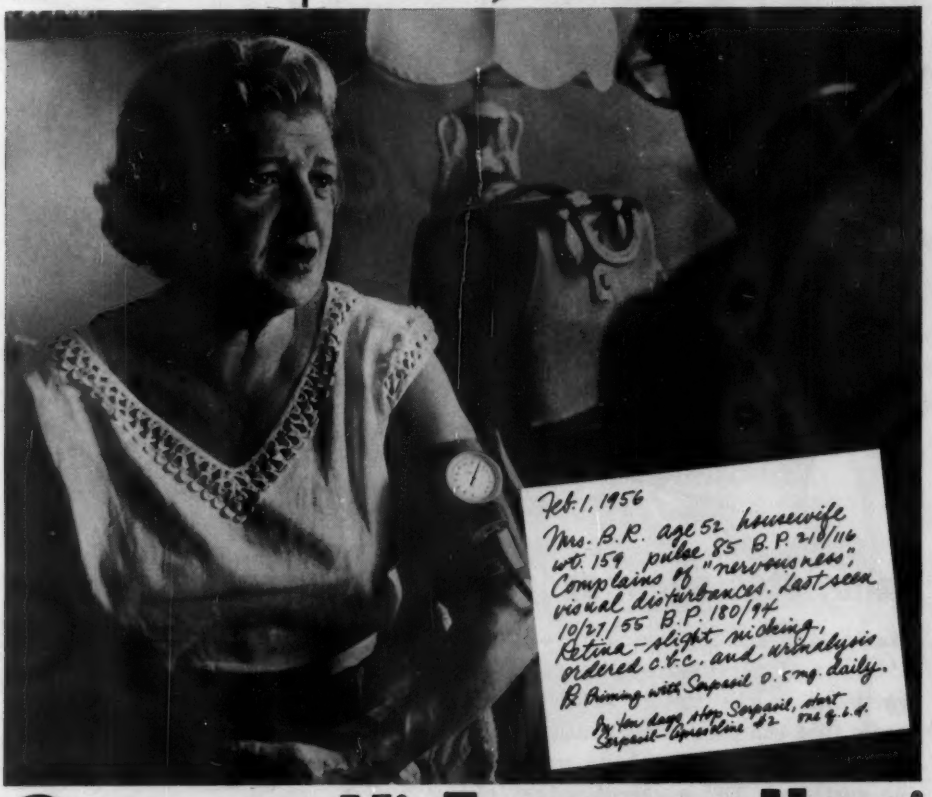
Feb. 1, 1956
Mrs. B.R. age 52 housewife
wt. 159 pulse 85 B.P. 218/116
Complains of "nervousness"
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10/27/55 B.P. 180/94
Retina – slight nicking,
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℞ Priming with Serpasil 0.5 mg. daily.
In few days stop Serpasil, start
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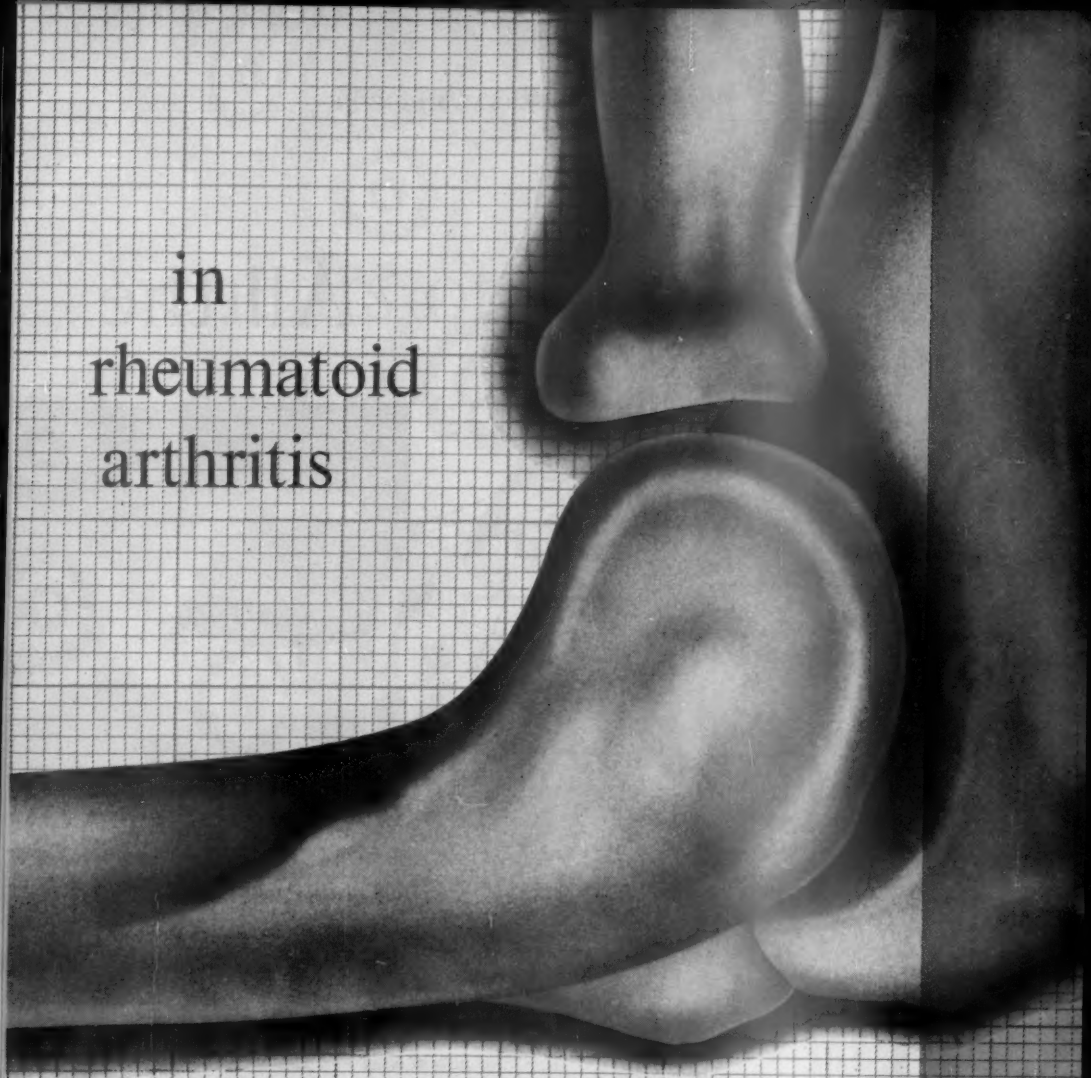

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1. Bollet, A. J., Black, R., and Bunim, J. J.: *J.A.M.A.* **158**: 459, June 11, 1955.

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1. Report of Study by Army, Navy, Air Force Motion Sickness Team: J.A.M.A. *160*:755 (March 3) 1956. ®Trademark

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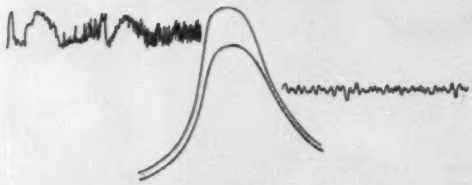

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". . . after the proper dose was established, 'Mysoline' was well tolerated without [serious] side effects."[3]

1. Doyle, P. J., and Livingston, S.: J. Pediat. *43*:413 (Oct.) 1953.
2. Livingston, S., and Petersen, D.: To be published.
3. Pence, L. M.: Texas State J. Med. *50*:290 (May) 1954.

LITERATURE ON REQUEST

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in epilepsy

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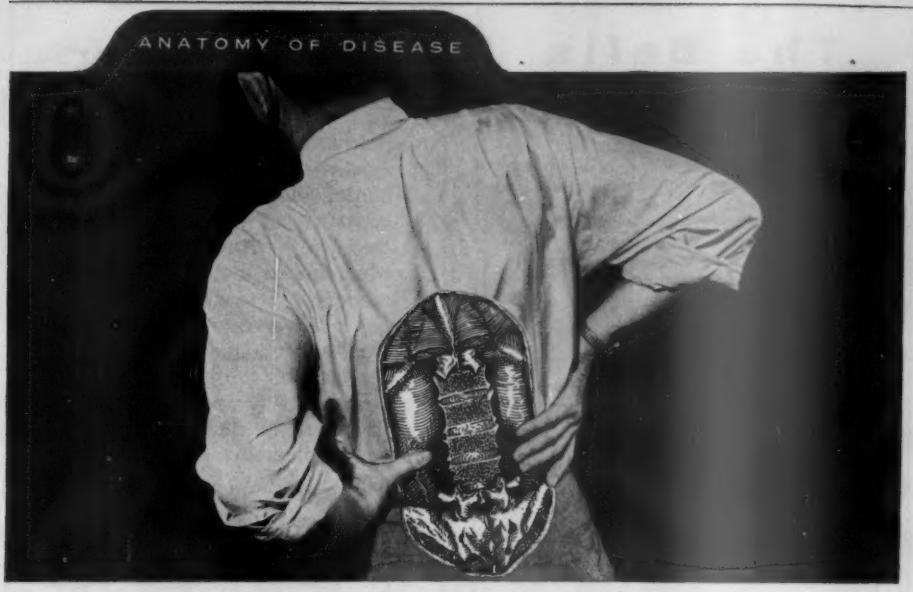

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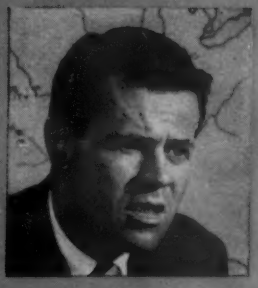

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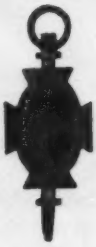

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FATAL AMEBIASIS: REPORT OF 148 FATAL CASES FROM THE ARMED FORCES INSTITUTES OF PATHOLOGY *

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INTRODUCTION

MOST authorities agree that the prevalence of amebiasis in the general population is approximately 10%,[1] and that the number of patients who develop fatal complications could be substantially reduced if there were greater awareness by the medical profession of the seriousness of the disease. The return of millions of servicemen from all parts of the world, some with subclinical amebic infection, has made this group of particular interest not only to the Armed Forces [2] but also to civilian physicians throughout the country.[3, 4, 5] It was thought valuable, therefore, to assemble the clinical and pathologic data on fatal cases of amebiasis available at the Armed Forces Institutes of Pathology.

Craig [6] and, more recently, Anderson, Bostick and Johnstone,[1] have published excellent texts reviewing the broader aspects of the disease and providing a satisfactory bibliography, so that no attempt has been made here to review the literature.

METHOD

Two hundred ninety cases of fatal amebiasis were filed at the Armed Forces Institutes of Pathology from 1862 to 1953. During this period over 500,000 pathologic specimens were registered. Of the 290 cases reviewed, 203 had records in which there were sufficient clinical and patho-

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logic data for our purposes. In 14 of these no definite cause of death was established, and in 41 others amebiasis was not primarily responsible for death but was discovered incidentally at autopsy. The remaining 148 cases were analyzed and are the subject of this report. Most of the rejected cases were dated prior to 1930. Many of the cases in this review were included in the smaller series reported by Radke in 1952.[7] Amebae were demonstrated in all cases, either in the intestines or liver at autopsy, or ante mortem in the stool or in aspirates of liver abscess.

A. Clinical Data

1. *Year of Death and General Incidence in Armed Forces*

Table 1 summarizes the distribution of the cases in our series from 1918 through 1952. The ratio of the average number of fatal cases to the average number of active personnel in the Armed Forces (in millions) for each year or period of years is also approximated.

Table 1

Year of Death and General Incidence in Armed Forces

Years	Deaths	Rate*	Years	Deaths	Rate*
1918–20	4	1.1	1945	37	4.5
1921–25	7	8.0	1946	11	5.8
1926–30	9	13.1	1947	4	4.0
1931–35	10	14.4	1948	3	2.1
1936–40	3	2.9	1949	7	4.3
1941	2	1.4	1950	9	6.2
1942	3	1.0	1951	11	3.4
1943	9	1.3	1952	4	1.1
1944	15	1.9		148	

* Average number of autopsied cases of fatal amebiasis per million persons on active duty in the U. S. Armed Forces per year.[8] The table is not completely accurate, since it excludes Navy autopsies before 1948 and includes some civilian and prisoner-of-war autopsies and Veterans Administration cases since 1948.

Within the limits of our method, it can be seen that the incidence of amebic deaths in the Armed Forces has been low and relatively constant since 1917, and that no definite trend is evident. This lack of progress would be more impressive if compared to the recent precipitous drop in mortality rate of some other once-common diseases, such as typhoid fever.[9] It should be noted that not every patient in the Armed Services who died of amebiasis is included in this series. Only the absence of a trend has statistical meaning in table 1.

2. *Sex and Age*

One hundred thirty-eight (93.2%) of the patients were males; 10 were females.

The age distribution in this study as seen in table 2 is characteristic of a military organization, although it is our impression that the distribution is weighted to the older age groups.[10]

One case involving a seven and one-half month old female is of interest, as fatal amebiasis is seldom reported in infants.[11, 12] This Panamanian infant was brought to the hospital soon after death without a clinical history. She was found to have multiple ulcers throughout the entire colon and rectum in which *Endamoeba histolytica* were numerous. There was no involvement of the liver or other organs.

3. *Nativity*

The birthplace of 87 of our patients was the United States, representing a large majority of the total. There were eight patients from Europe and North Africa, six from Central America, eight from the Philippines, eight from China, six from Korea, and one each from Japan and Indo-China. In 23 cases there was no statement of nativity.

TABLE 2

Age

Age	Cases
Under 20 years	5
20 to 25 years	27
26 to 30 years	27
31 to 40 years	40
41 to 50 years	18
51 to 60 years	15
Over 60	5
Not stated	11
Total	148

Race, not indicated in our study, may play a prominent part in the development of serious amebiasis. When natives in various parts of the world are compared with visitors, or foreign residents, the non-natives are said to be more susceptible to the disease.[13] Elsden-Dew and his associates, however, suggest that in the development of severe intestinal amebiasis and its fatal complications [14] the economic and dietary status of the patients may be much more important than either the nationality of the patients or the "pathogenicity" of organisms.

4. *Area of Acquisition of Amebiasis*

It is impossible in many instances to determine where the amebic infections were acquired. This is due to the frequent movements of personnel characteristic of the Armed Forces, and also to the 10% prevalence of the disease in our general population, which makes it difficult to exclude preëxisting, subclinical infection.

In table 3 have been listed the geographic areas where amebic infection

was apparently contracted. The Far East area contributed almost nine times as many cases as did Europe.

The relatively large number of cases from the Philippines and the Canal Zone are reflections of military activities in those areas for a 50 year period. It may be of interest that in more than one third of our cases of fatal amebic infection, the infection was acquired in the continental United States.

5. *Duration of Symptoms before Death*

The onset of the disease in most of the cases was acute, the clinical course was fairly rapid, and progression to death was swift. Data as summarized in table 4 indicate that almost four fifths of the patients died within six months of their first reported symptoms, and, of these, 20% died within two weeks. This is in striking contrast to the popular notion, based on the majority of nonfatal cases, that amebiasis is a chronic quiescent infection. There was no marked difference between the group that developed liver

TABLE 3

Area of Acquisition of Amebiasis

	Cases
United States	50
Philippines	30
Other Pacific, including Japan, Alaska	20
China-Burma-India	11
Korea	8
North Africa	8
Canal Zone (Panama)	7
Europe	8
Abroad (exact locale not stated)	6
	148

abscesses and the group that did not. However, the 28 patients dying with amebic liver abscess within four weeks of the onset of symptoms indicate that previous intestinal symptoms and a one to three month latent period are not to be relied on in the differential diagnosis of this dangerous complication.[13]

6. *Clinical Diagnosis*

Amebiasis was correctly diagnosed in 48, or 36%, of the 133 cases in which a clinical diagnosis was recorded. Nonspecific or inadequate diagnoses were made in 47% and included liver, lung or brain abscess, hepatitis, dysentery, enteritis, peritonitis, perforation, hemorrhage and obstruction. Incorrect diagnoses were made in 17% of the cases, and included liver carcinoma (twice), ulcerative colitis (five times), appendicitis (five times), gastrointestinal carcinoma (four times), gall-bladder disease (twice), and pneumonia, trauma, hemorrhoids and brucellosis (once each).

Liver disease was suspected in 84% (47 of 56) of those patients in whom the amebic liver abscess led directly to death. Fifty per cent of the liver

abscesses, however, were not diagnosed in the cases in which those lesions were found at autopsy. Carcinoma of the bowel was the wrong diagnosis in only six cases and appendicitis in only five, as compared to much higher numbers in other series.[15, 16, 17]

7. Specific Treatment

Forty-five patients were given specific chemical therapy, and a moderate number received surgical drainage or operation. The correlation between correct diagnosis and specific therapy was, surprisingly enough, not great. Emetine, alone or in combination, was given in 84% of those treated.

In 89 cases the patients received no specific antiamebic therapy, and in another 14 the type of therapy, if any, was not stated. Emetine alone was received by 16 patients, emetine and Carbarsone by eight, and emetine and

TABLE 4

Duration of Symptoms before Death

	Cases without Liver Abscess	Cases with Liver Abscess	Total
Under 2 weeks	9	11	20
2 to 4 weeks	9	17	26
4 weeks to 2 months	4	9	13
2 to 6 months	13	27	40
6 months to 2 years	6	8	14
2 to 5 years	5	3	8
6 to 10 years	1	2	3
11 to 20 years	1	1	2
Over 20 years	0	0	0
Not stated	10	12	22
	58	90	148

Diodoquin by eight. Thirteen patients received various other combinations of drugs, with or without emetine, including Diodoquin, Carbarsone, chiniofon, Aureomycin, chloroquine and Chloromycetin.

The effect of specific therapy on the prevention or cure of liver abscesses could not be determined by an evaluation of our data.

B. PATHOLOGIC DATA

1. Specific Cause of Death

The specific or predominating causes of death in this series of cases have been summarized in table 5. It can be seen that, of the entire series, 80 patients (54%) died of intestinal complications, 31 (21%) of liver disease, 17 (11.5%) with fatal lung involvement, and 10 as an aftermath of surgical intervention. Six patients had an "amebic" brain abscess, although in only

two cases was the amebic etiology established unequivocally. Four died of heart failure (two with amebic pericarditis and two with myocarditis probably due to emetine toxicity).[18, 19, 20, 21]

Perforation of the intestine with peritonitis was the most common cause of death (45 cases), and peritonitis from all causes was fatal to 75 patients (51%). In the group without liver abscesses, the death was accompanied in 20 cases by associated conditions, including pneumonia (six), tuberculosis (two), cirrhosis (two), and 10 other conditions, as follows (one each):

TABLE 5

Specific Cause of Death

	Total	With Peritonitis*
a. Intestinal		
Perforation	45	45
Dysentery	21	5
Hemorrhage	5	0
Abscess	2	2
Obstruction	1	0
Surgery	6	3
	80(54%)	55
b. Liver abscess		
Without rupture†	19	4
Rupture into abdomen	12	11
Lung involvement‡	17	2
Pericarditis	2	0
Subdiaphragmatic abscess	2	0
Surgical drainage	4	1
	56(38%)	18
c. Miscellaneous		
Brain abscess	6	0
"Emetine myocarditis"	2	0
Other	2	0
	10(7%)	0
d. Not stated	2(1%)	2
	148	75(51%)

* Cases in which peritonitis was the immediate cause of death.
† Three died of liver insufficiency, two of pleurisy.
‡ Empyema was the precipitating cause of death in nine of these.

malaria, hookworm disease, ascariasis, auricular fibrillation, myocarditis, encephalitis, hemorrhage, pleural effusion, malnutrition and wounds. In these cases amebiasis was considered to be the primary cause of death, but the above conditions were listed as "contributory."

In the group without liver abscess or apparent amebic liver infection there were eight cases in which "hepatitis" was recorded. The liver findings at autopsy in these cases were varied, consisting of acute yellow atrophy, infectious hepatitis, jaundice with chronic portal inflammation, hepatocel-

lular degeneration, or severe central necrosis. No amebae were found and no diagnosis of diffuse amebic hepatitis could be made.

Jaundice was noted in approximately 14% of both the cases with liver abscess and those without abscess. Specifically, of the 90 cases in which liver abscesses were found, 13 had jaundice (14.4%), 14 definitely had no jaundice, and 63 had no statement about jaundice. Of the 58 cases without abscesses in the liver, eight (13.8%) had jaundice, 12 had no jaundice, and 38 had no statement about jaundice. Most of the cases in which no statement was made probably did not have jaundice. It would appear, therefore, that the jaundice in patients with fatal amebiasis may not be related to the presence or absence of hepatic abscesses but may be caused by other factors, possibly intestinal ulceration or peritonitis.

TABLE 6
Intestinal Lesions

Location of Principal Involvement	Distribution		Perforation Number
	Number	Per Cent	
Entire colon (multiple)	60	40.5	9
Cecum and terminal ileum	7	4.7	—
Cecum alone	21	14.2	19
Appendix	0	0.0	2
Cecum, ascending colon	14	9.5	—
Ascending colon	6	4.1	4
Transverse and descending colon	4	2.7	7
Rectosigmoid	11	7.4	5
Subtotal	123	83.1	46
Absent intestinal lesions			
Liver abscess only	12	8.1	
Liver abscess and lung involvement	3	2.0	
Liver and brain abscess	2	1.4	
Liver abscess into pericardium	1	.7	
Subtotal	18	12.2	
Not stated	7	4.7	13
Total	148	100.0	59(40%)

2. *Intestinal Lesions*

Location of Principal Involvement: The entire colon was extensively involved in almost half of the cases with intestinal lesions (table 6). In decreasing order of frequency were the cecum, cecum and ascending colon, rectosigmoid, cecum and terminal ileum, ascending colon (alone), and transverse and descending colon. The terminal ileum was involved in seven cases which also had extensive colonic parasitization. This distribution of lesions is in harmony with the classic report of Clark.[22]

In a recent report based on biopsy and autopsy material, no histologic support for the clinical concept of diffuse amebic hepatitis was found.[29]

Intestinal perforation was found in 52% of the cases without liver abscess and in 32% of those with liver abscesses, totaling 59 cases. The most frequent site was the cecum, with the "entire" colon (multiple perforations), the transverse and descending colon, the rectosigmoid and the ascending colon involved in decreasing frequency. Only two cases of appendiceal rupture were noted; however, a considerable number of patients had had previous appendectomy.

Severity: In the 58 cases without liver abscess, the incidence of severe intestinal lesions as measured on a 1 to 4 plus scale ran as follows: 1 plus, no cases; 2 plus, 12 cases; 3 plus, 16 cases; 4 plus, 23 cases; in seven cases no estimate could be made. However, those cases with a liver abscess generally had milder intestinal amebiasis with 1 plus, 12 cases; 2 plus, eight cases; 3 plus, 20 cases; 4 plus, 23 cases; in 27 cases insufficient data were available for estimate.

Absence of Intestinal Lesions: There were 18 cases (12.2%) in which there were no detectable lesions in the intestine (table 6). It is of interest

TABLE 7

Amebae Found Histologically in the Intestine

	Specific Therapy	No Therapy	Not Stated	Total
Amebae found	12	31	6	49
Amebae not found	18	11	1	30
No lesions	10	5	3	18
Not stated	5	42	4	51
Total	45	89	14	148

that one third of these patients had unusual and dangerous complications of the disease. Three had extension of the liver abscess into the pleural cavity and lung, and one into the pericardium. Two cases had solitary amebic brain abscesses (one equivocal) in addition to their liver abscess.

Amebae Found Histologically in the Intestine: E. histolytica was demonstrated in the histologic sections at autopsy in one third of the cases, and was not found in one third (table 7). No statement was made in the remaining third. Specific therapy had been received in a highly significant number of those histologically sterile ($X^2 = 9.9$, $P = < 0.01$).

3. *Hepatic Abscesses*

Number and Location: As shown in table 8, 90 (61%) of our cases had amebic abscesses in the liver, a proportion considerably higher than that previously found.[23] It is possible that this high proportion may be due to weighted selections of cases, since greater effort may have been made to perform autopsies on those cases with liver abscess.

Of the 90 liver abscess cases, 36 (40%) had a single abscess in the right

TABLE 8
Hepatic Abscesses

Number of Abscesses	Right Lobe	Left Lobe	Both Lobes	Not Stated	Total
One	36	4	3	3	46(51%)
Multiple	9	0	24	10	43(48%)
Not stated	1	0	0	0	1
Total	46(51%)	4(4%)	27(30%)	13(14%)	90

lobe and 24 (27%) had multiple abscesses throughout all lobes. Of the remaining one third, nine had two or more abscesses in the right lobe, four had a single abscess in the left lobe, three had a single abscess in both lobes, and in 14 the information was incomplete. The abscesses varied in size from a few millimeters up to an entire lobe.

Rupture: Of 41 liver abscesses that ruptured, 22 extended into the lung, 10 into the abdominal cavity, five under the diaphragm, two into the pericardium, and one each into the kidney and pancreas.[24]

TABLE 9
Amebae Found Histologically in the Liver Abscesses

	Specific Therapy	No Therapy	Not Stated	Total
Amebae found	9	38	6	53(60%)
Amebae not found	19	13	3	35(39%)
Not stated	0	2	0	2
Total	28	53	9	90

The influence of secondary infection upon rupture could not be determined. Ten cases showed pleurisy without apparent rupture or subdiaphragmatic extension, and two had peritonitis without apparent intestinal or hepatic rupture.

Amebae Found Histologically in the Liver Abscesses: Amebae were demonstrated in 60% of 88 of the 90 cases of liver abscess for which information was furnished as to the presence or absence of amebae (table 9).

TABLE 10
Correlation between Intestinal and Hepatic Location of Amebiasis

Intestinal Location	Right Lobe	Left Lobe	Both Lobes	Total	Distribution for Entire Series
Right colon only	18	2	8	28	43
Left colon only	2	0	1	3	11
Entire colon	20	1	10	31	60
None	6	1	8	15	—
Total	46	4	27	77	114

This is a comparatively high detection rate.[25] As in the intestinal examination, specific therapy had been received in a highly significant number of those histologically sterile ($X^2 = 11.7$; $P = 0.01$).

Correlation between Intestinal and Hepatic Location of Amebiasis: As can be seen in table 10, there is no correlation, case for case, between the location of the intestinal lesion and the location of the liver abscess. Some correlation might be predicted from the observation that blood from the right colon (drained by the superior mesenteric vein) flows predominantly into the right liver lobe, and that blood from the left colon (drained by the inferior mesenteric vein) flows predominantly into the left lobe.[26] There were 18 cases of amebic liver abscess entirely without intestinal lesions at the time of autopsy.

Liver Weights: If 2,000 gm. is generously taken as the upper limit of "normal," there were 52 livers of normal size (24 without abscess, 28 with abscess); 48 enlarged livers (10 without abscess, 38 with); and 48 livers for which no statement was made (table 11). Of the 100 livers for which weights were given, 10% were enlarged without hepatic abscess and 28% were "normal" with demonstrable abscess.

TABLE 11

Liver Weights

	Without Liver Abscess	With Liver Abscess
Under 1,000 gm.	1*	0
1,000–1,250 gm.	3	3
1,250–1,500 gm.	6	4
1,500–1,750 gm.	5	11
1,750–2,000 gm.	9	10
2,000–2,250 gm.	5	4
2,250–2,500 gm.	2	9
2,500–3,000 gm.	3	11
3,000–4,000 gm.	0	8
4,000 gm. or over	0	6†
Weight not stated	24	24
Total	58	90

* Infant liver, 125 gm.
† Maximum, 6,500 gm.

These data may be of value in consideration of *hepatomegaly* in cases of so-called amebic hepatitis.[27, 28, 29] Comparative liver weights were obtained from 34 random cases of death due to peritonitis in adults at the New York Hospital since 1943 (excluding cases with cirrhosis, liver tumor or acute liver atrophy). The age and sex ranges of the "control" group, though not identical, were sufficiently close for purposes of comparison. Failure to find enlarged livers in this group (only four greater than 2,000 gm.) demonstrates that the hepatomegaly seen in fatal amebiasis was not associated with peritonitis alone.

Summary

Clinical and pathologic data on 148 cases of fatal amebiasis collected from the files of the Armed Forces Institutes of Pathology were compiled.

1. Although deaths due to amebiasis were not common in the Armed Forces, there is no indication of significant progress in lowering the mortality rate.

2. Fatal amebiasis occurred predominantly in older active adult males.

3. The case of a seven and one-half month old Panamanian female is briefly reported.

4. Although over one third of the cases of fatal amebiasis were acquired in the Far East, it is worthy of note that in another third the infection was acquired in the continental United States.

5. The progression of amebiasis from onset of symptoms to death was rapid and fulminating in this series, with four fifths of the patients dying within six months of their first symptoms and two fifths succumbing within two months.

6. Amebiasis was correctly diagnosed in only one third of our cases. Liver abscesses were missed clinically in one-half of 90 cases in which the lesion was present.

7. Emetine, alone or in combination, was given in 84% of the 45 cases receiving specific therapy. Surgical complications were responsible for 10 deaths.

8. The significant causes of death in our series were, in decreasing order, intestinal perforation and peritonitis, uncomplicated dysentery, liver abscess without rupture, and amebic lung abscesses. Peritonitis occurred terminally in over one-half of the cases. Jaundice was present in 14% of cases both with liver abscess and without abscess. No instance of diffuse amebic hepatitis was found.

9. The location of intestinal lesions was in harmony with previous reports. In decreasing frequency, the entire colon, the cecum, the ascending colon and the rectosigmoid colon were significantly involved. The cecum perforated in a conspicuous proportion of the 59 cases with this complication. No intestinal lesions were found in 18 cases. Amebae were found histologically in one third of the cases, most of which had not received specific therapy.

10. Amebic liver abscesses were found in 61% of our cases, over half of which had abscesses in the right lobe alone. Forty-one abscesses ruptured from the liver into the lung, abdominal cavity, sub-diaphragmatic area, pericardium, kidney or pancreas, in decreasing frequency. Amebae were demonstrated histologically in 60% of the liver abscesses. There was no correlalation, case for case, between the location of the intestinal lesions and the location of the liver abscesses. Hepatomegaly was found in a significant number of livers in which neither large abscesses nor "hepatitis" was demonstrated.

SUMMARIO IN INTERLINGUA

Datos clinic e pathologic in 148 casos de amebiasis mortal esseva colligite ab le archivos del Instituto Pathologic del Fortias Armate. Le sequente observationes pareva significative.

1. Amebiasis mortal occurreva predominantemente in masculos active de etates avantiate. Plus que un tertio del casos habeva essite acquirite in le Statos Unite continental. Il habeva nulle signo de progresso significative in reducer le mortalitate.

2. Le progresso de amebiasis, ab le momento del declaration del symptomas usque al morte, esseva rapide e fulminante. Quatro quintos del patientes moriva intra sex menses post le declaration del prime symptomas, duo quintos intra duo menses. Le diagnose de amebiasis esseva establite correctemente in solmente un tertio del casos mortal. Abscessos hepatic esseva presente in 90 casos, sed lor identification per medios clinic succedeva in solmente un medietate de ille gruppo.

3. Le significative causas de morte esseva perforation intestinal e peritonitis, dysenteria non-complicate, abscesso hepatic sin ruptura, e abscesso amebic del pulmone. Peritonitis in occurrentia terminal characterisava un medietate del casos.

4. Le locos del lesiones intestinal esseva simile a illos describite in previe reportos. Le integre colon, le ceco, le colon ascendente, e le rectosigmoide esseva involvite de maniera significative. In un conspicue portion del 59 casos con perforation intestinal, le sito de iste lesion esseva le ceco. Nulle lesiones intestinal esseva trovate in 18 del casos mortal.

5. Amebic abscessos hepatic esseva trovate in 61 pro cento del casos. Plus que un medietate de istos habeva abscessos solmente in le lobo dextere. Un total de 41 del abscessos rupturava ab le hepate a in le pulmone, le cavitate abdominal, le area subdiaphragmatic, le pericardio, le ren, o le pancreas (con frequentias decrescente). Amebas esseva demonstrate histologicamente in 60 pro cento del abscessos hepatic. Nulle correlation esseva constatate inter le loco del lesiones intestinal e le loco del abscessos hepatic in le casos individual. Hepatomegalia esseva trovate in un significative numero de hepates in que ni grande abscessos ni "hepatitis" esseva demonstrabile. Nulle caso de diffuse hepatitis amebic esseva trovate.

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A MEDICAL APPRAISAL OF TRANSAORTIC COMMISSUROTOMY *

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Introduction

The first surgical method to correct commissural fusion of rheumatic aortic stenosis was conceived and employed by Bailey in 1950.[1] It was termed transventricular commissurotomy, because the operation required an entrance into the left ventricular cavity through its muscular wall for the passage of a dilator which engaged the valve from below and forcefully separated the leaflets.

The recent review by Likoff and associates [2] of the clinical results of this technic in 79 patients, 65 of whom had aortic stenosis alone or combined with adynamic aortic regurgitation, reported an immediate operative mortality of 18% when the stenosis was not associated with other significant valve defects, and cited ventricular fibrillation as the most frequent cause of death. The clinical improvement after surgery was most encouraging, but it was tempered by a dynamic aortic regurgitation produced in 7% of the survivors.

It has been reasonable to suspect that these unpredictable deterrents to the growing promise of the surgical management of aortic stenosis originated in large measure from the operative technic which required direct trauma to the hypertrophied left ventricular myocardium, and did not allow the surgeon to control the dilator digitally at the very site of its critical application.

In the interest of avoiding these patent weaknesses, and what appeared to be their unfavorable consequences, the transaortic commissurotomy was developed.[3] This procedure avoids myocardial injury by permitting the surgeon to enter the lumen of the aorta through an artificially created pouch, and to reach the valve without unusual blood loss in order to split the commissures under direct digital guidance (figure 1).

The present study analyzes the clinical experience with this technic in 40 patients operated on for significant rheumatic aortic stenosis, and compares the results with those of transventricular commissurotomy.

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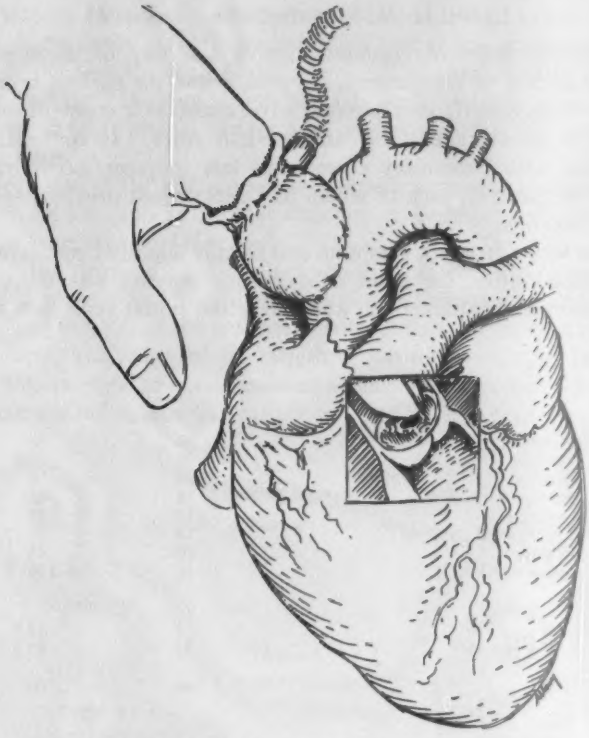

FIG. 1. The technic of transaortic commissurotomy.

MATERIAL (TABLE 1)

The 40 patients treated surgically during the interval from March, 1953, to January, 1955, consist of 34 males and six females, ranging in age from 25 to 60 years, who had aortic stenosis alone (Group I), or in combination with adynamic, physiologically insignificant aortic regurgitation (Group II). None of these patients had previous cardiac surgery.

TABLE 1

Anatomic-Physiologic Diagnosis and Patient Material

Group	Diagnosis	No. of Patients	Male	Female	History of Rheumatic Fever
1	AS	22	19	3	9
2	As, ai	18	15	3	2
Totals		40	34(85%)	6(15%)	11(27.5%)

Capital letters refer to significant lesions.

Clinical Manifestations (Table 2)

The specific onset of rheumatic activity or any of its stigmata was recalled by 27.5% of the patients. *Dyspnea* was the earliest symptom and the one most frequently encountered. It existed as a constant and serious complaint for an average of two and one-half years. In contrast, paroxysmal dyspnea with pulmonary edema was less frequent, occurring in only 30.2% of the patients, each of whom had experienced previous shortness of breath on exertion.

Fatigue was a frequent symptom and usually appeared concurrently with, or immediately after, the onset of dyspnea. *Angina* was the third most common complaint, although it was rarely the initial issue and was never

Table 2

Clinical Manifestations

	No. of Patients	% of Total
Dyspnea	34	85
Fatigue	29	70.2
Angina	20	50
Vertigo	18	45
Syncope	14	35
Paroxysmal dyspnea	13	30.2
Edema	10	25
Sinus rhythm	40	100
A^2		
Normal	7	17.5
Decreased	33	82.5
Thrill	40	100
Heart Size		
Normal	0	0
1 Plus	7	17.5
2 Plus or more	33	82.5
Electrocardiogram		
Normal	6	15
Left ventricular hypertrophy	26	65
Bundle branch block	3	7.5
Coronary patterns	5	12.5

observed as an isolated manifestation. The frequency or severity of the pain of coronary artery insufficiency was not related to the age of the patient.

Vertigo was reported by 45% of the patients, and *syncope* by 35%. The attacks of unconsciousness were completely unpredictable and occurred without relation to exercise.

Peripheral edema finally developed in 25% of the patients. No individual in the entire group reported hemoptysis or peripheral embolization.

Normal sinus rhythm was present in each patient. The *blood pressure levels* were consistently within normal limits. The mean pulse pressure in the group with isolated aortic stenosis did not differ materially from the value recorded in those with coexistent adynamic aortic insufficiency.

There was no exception to the finding of a loud, rough systolic murmur at the base of the heart. In all but seven patients this was accompanied by an absent or decreased second aortic sound. The basal systolic thrill was a constant finding. A faint, high pitched, early diastolic murmur was audible along the left sternal border and in the second right interspace in 45% of the patients.

The x-ray size of the left ventricular outflow tract was increased 2 plus or greater in 82.5%, and in the vast majority of these patients enlargement of the inflow tract was also observed.

Of the entire group, all but six had abnormal electrocardiograms. The most common pattern was that of left ventricular hypertrophy and "strain," which appeared in 65% of the patients. Intraventricular conduction defects were infrequent, and appeared in only three patients. In spite of the frequency of angina, specific abnormalities suggestive of coronary artery disease were recognized in only five instances.

TABLE 3

Operative Mortality

Group	No. of Patients	Deaths	% Mortality
1 (AS)	22	2	9
2 (AS, ai)	18	2	11
Totals	40	4	10

TABLE 4

Causes of Death

Causes of Death	No. of Patients	Time Relation
Detachment of aortic cusp	1	Immediate
Ventricular fibrillation	1	Immediate
Hemorrhage	1	Immediate
Cerebral embolism	1	Six hours

The *brachial artery tracing* was abnormal in 18 patients in whom the test was performed. The variations consisted of an interruption in the upstroke or anacrotic limb of the curve in five patients (26%), a true anacrotic notch in nine patients (50%), and other alterations in the tracing in two patients (11%). The peak of systole was delayed beyond the normal limits of 0.06 to 0.09 second after the onset of ejection in all patients, and ranged from .10 to .28 second.

OPERATIVE MORTALITY (TABLE 3)

The operative mortality was 10%. The immediate causes of death and the time relation of the operation to death are listed in table 4.

One of the four deaths was the result of a technical error in which the right anterior cusp was detached from the annulus for a distance of 1 cm. An immediate and lethal aortic regurgitation followed.

Ventricular fibrillation developed in two patients during or immediately after the commissurotomy. In one of these, however, the fatal arrhythmia was secondary to profuse hemorrhage.

Although a cerebral embolism was responsible for the death of the fourth patient six hours after a successful commissurotomy, necropsy also revealed a severe degree of coronary sclerosis not suspected previously.

Postoperative Hospital Course (Table 5)

Cardiac complications without mortality occurred in 13 (36.1%) of the survivors. *Atrial fibrillation* developed in seven patients (19.4%) during the first postoperative week. The rhythm was reverted to a normal

Table 5

Postoperative Hospital Complications

Type	No. of Patients	% of Total (36)
Cardiac		
Congestive failure	6	16.6
Atrial fibrillation (converted)	5	13.8
Atrial fibrillation (permanent)	2	5.5
Totals	13	36.1
Pulmonary		
Pleural effusion	11	30.5
Retained secretions	6	16.6
(Requiring bronchoscopy)	—	—
Totals	17	47.2
Miscellaneous		
S.B.E.	1	2.7
Psychosis	1	2.7
Lower nephron nephrosis	2	5.5
Uremia	1	2.7
Embolic issue	1	2.7
Totals	6	16.6

sinus mechanism in five of these patients with ordinary doses of quinidine sulfate. The remainder were resistant to the initial treatment and were discharged with atrial fibrillation as the dominant rhythm.

Congestive heart failure occurred in six patients (16.6%), but this responded to an adjusted regimen, including salt restriction and the use of mercurial diuretics. Cardiac compensation was firmly established in each instance at the conclusion of hospitalization.

Subacute bacterial endocarditis due to coagulase-negative *Staphylococcus aureus* occurred in a single patient and required rigorous antibiotic therapy before apparent clinical and bacteriologic cure was accomplished.

Pulmonary complications without death were encountered in 17 of the patients (47.2%). However, these included a simple right pleural effusion in 11 patients and retained secretions in the remaining six.

TABLE 6

Duration of Follow-Up Review (in Months)

Months Since Surgery	No. of Patients
3–5	14
6–8	6
9–11	1
12–15	6
Total	27

Miscellaneous complications included acute renal insufficiency, peripheral embolization and toxic psychosis.

FOLLOW-UP REVIEW

The postoperative evaluation was limited to patients operated upon at least three months previously, and includes 27 individuals, six of whom had been observed for 12 months or longer (table 6). In this analysis, late deaths, symptomatic improvement and alterations in objective manifestations are considered separately.

Late Deaths: Six patients (*22.2%*) died after discharge from the hospital. The intervals between surgery and death and the causes, if established definitely, are listed in table 7.

The immediate cause of death was not determined in the two patients who died suddenly, although an acute onset of ventricular fibrillation secondary to coronary artery insufficiency must be suspected.

Of the four patients who succumbed to subacute bacterial endocarditis, the diagnosis in one was reached during the immediate postoperative period, and a bacteriologic and clinical cure was believed to have been accomplished during the hospital stay. In a second patient the diagnosis was suspected within a week after operation because of a low grade febrile reaction which did not respond to antibiotic therapy. The initial blood culture was positive, but this result was considered unreliable because all of the multiple subsequent cultures were negative.

In the remaining two patients there was no clinical reason to suspect subacute bacterial endocarditis during the postoperative hospitalization. However, a positive blood culture developed in one only 79 days after

TABLE 7

Late Deaths

Case No.	Cause of Death	Time After Surgery
1	S.B.E.	2 months
2	S.B.E.	3 months
3	S.B.E.	4 months
4	S.B.E.	14 months
5	Unknown (sudden)	5 months
6	Unknown (sudden)	14 months

surgery. The offending organism in three patients was coagulase-negative *Staph. aureus,* and in the fourth, Friedländer's bacillus.

To summarize these experiences, subacute bacterial endocarditis was the most common cause of death after the patient recovered from the operation and was discharged from the hospital. However, in one-half of the patients afflicted, the disease had its actual onset very shortly after surgery and either was unrecognized or responded only temporarily to treatment. In each instance the offending organism was unusual and resistant to ordinary therapy.

Symptomatology (Table 8)

If generic and nonspecific terms are applied to the over-all symptomatic pattern, 15 (71.4%) of the living patients may be classified as "improved," four (19%) as "worse," and two (9.5%) as "unchanged."

Table 8

Effect of Transaortic Commissurotomy on Clinical Manifestations

	Present Preoperatively	Postoperative Status			
		Absent	Improved	Same	Worse
Dyspnea	19	9	3	4	3
Fatigue	16	6	5	3	2
Angina	9	8		1	
Vertigo	9	6		3	
Syncope	9	7	1	1	
Paroxysmal dyspnea	7	5	1		1
Edema	5	3		1	1
Normal sinus rhythm	21				

An inquiry into the causes of an unchanged or deteriorating clinical pattern is useful in determining the scope of surgery for aortic stenosis, and in estimating the limitations of the transaortic operation.

Of the four patients with more serious symptomatic manifestations, two had dynamic aortic regurgitation produced at the time of surgery. One of the remaining patients obtained an excellent mechanical result but became pregnant shortly after operation and, although a full term delivery was accomplished successfully, never regained her former degree of clinical comfort.

The morphology of the valve imposed severe limitations upon the efforts of the surgeon in the additional patient who was worse after transaortic commissurotomy and in the two who remained unchanged. In each instance the leaflets were heavily calcified, and a minimal increase in the size of the aortic orifice resulted from the operation.

Of the 19 patients who had experienced significant dyspnea prior to operation, 12 (63.1%) either no longer had the complaint or were markedly

improved under normal activity. Nocturnal dyspnea did not recur in five of the seven patients (71.3%) in whom it had been a prominent symptom.

Fatigue, a major issue in 16 patients, disappeared or was ameliorated considerably in 11 (66.7%). Angina no longer was present in eight of the nine patients (88.8%) in whom it had been a disabling complaint.

During the period of the follow-up review, syncope did not recur in seven of the nine patients (77.7%) previously afflicted, and vertigo disappeared in six of nine patients (66.6%) who had presented the symptom as a major disability.

Although edema had been present in five patients at some period prior to operation, it had been controlled in each instance at the time of surgery. No recurrence was observed in three of these individuals (60%).

Objective Manifestations

The classic findings of dynamic aortic regurgitation were discovered in two patients, an incidence of 5.5% in those who survived surgery and of 7.4% in the follow-up group. When individuals with this complication were eliminated, no significant change was noted in the mean blood pressure values after operation.

Table 9

Effect of Transaortic Commissurotomy on Auscultatory Findings

Finding	No. Present Preoperatively	Postoperatively			
		Increased	Same	Diminished	Produced
Aortic systolic murmur	21	1	9	11	
Aortic diastolic murmur	11	2	9		5
Diminished or absent aortic second sound	21	12	9		

In 11 (52.3%) the rough aortic systolic murmur was reduced in intensity, and in 12 (57.1%) the second sound was more distinct (table 9). An early, blowing diastolic murmur appeared in five of 10 patients (50%) in whom it had not been present previously. In one of these, dynamic regurgitation was produced. The murmur was exaggerated in two of 11 patients (18.1%) who had had the finding preoperatively, and in one, significant regurgitation was created by the surgery.

Otherwise stated, transaortic commissurotomy beneficially modified the the auscultatory signs characteristic of aortic stenosis in one of every two patients, produced the murmur of aortic regurgitation in a like percentage when it had not been present previously, and exaggerated an existing murmur of regurgitation in approximately one of every six cases. Furthermore, the diastolic murmur was more apt to indicate serious aortic regurgitation when it had been increased rather than initially produced by surgery.

TABLE 10
Effect of Transaortic Commissurotomy on Heart Size

Heart Size	Preoperative No. of Patients	Postoperative No. of Patients
1+	3	4
2+	13	9
3+	4	7
4+	1	1
Totals	21	21

Prior to surgery, five of the 21 patients (23.8%) included in the follow-up survey had a heart size of grade 3 or more as determined by x-ray examination (table 10). This was increased to eight patients (38%) after surgery. The difference probably is not significant, because marked alterations in heart size were not encountered, the greatest change being from grade 2 to grade 3 enlargement in three patients. Other than the two patients in whom dynamic aortic regurgitation was produced, there was no apparent correlation between the radiologic increase in size and the clinical result.

Significant alterations were not noted in the electrocardiographic patterns, even when these observations were made 15 months after commissurotomy.

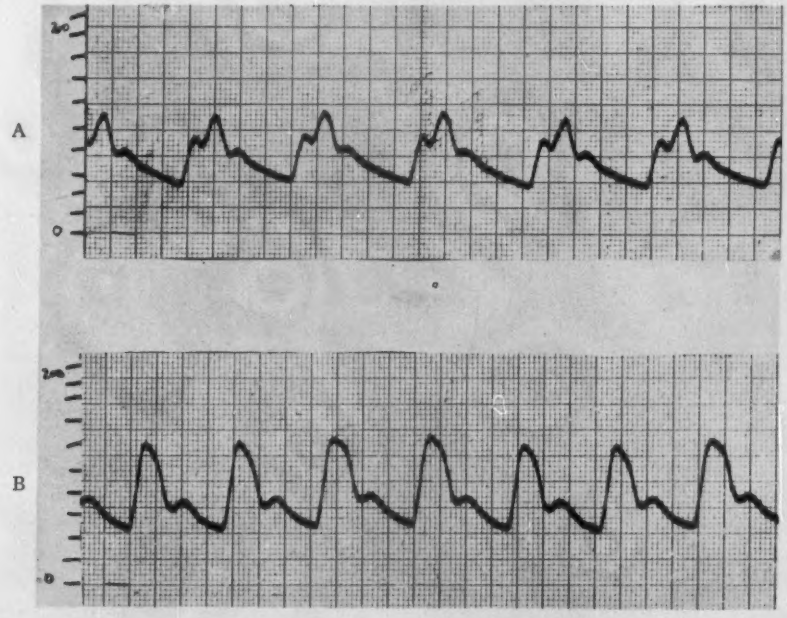

FIG. 2. Brachial artery tracing: A. pretransaortic and B. post-transaortic commissurotomy. Note disappearance of anacrotic notch following surgery.

Following surgery, the brachial artery tracing was repeated in each of the 18 patients studied preoperatively. Because of both sharp differences in cardiac rate and mechanical difficulties, two of the tracings could not be compared with previous graphs. No alteration was noted in five patients (31%). Six of the remaining 11 (37% of the total studies compared) were unequivocally improved as defined by a shortened systolic ejection time and the disappearance or marked alteration in the position of the anacrotic notch (figure 2). The ejection time was improved in three others. However, in these and in two additional patients, in whom only the anacrotic

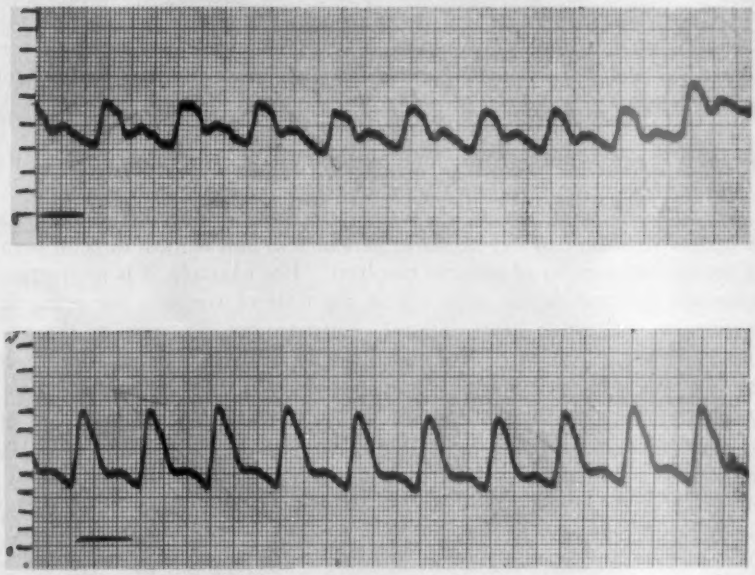

FIG. 3. Brachial artery tracing: A. pretransaortic and B. post-transaortic commissurotomy. Note position of dicrotic incisura following surgery.

notch was altered, a lower dicrotic incisura suggested the presence of aortic regurgitation (figure 3).

It is interesting to note that the intensity of the aortic sound increased sharply in four of the six patients in whom the brachial artery tracing was considerably improved. However, the sound was not increased in a single case when the tracing remained the same or became worse. Furthermore, five of the six with improved brachial artery curves enjoyed impressive clinical benefit, but none of those in whom the tracing appeared worse had the same good fortune. Actually, in this latter group two patients had more severe symptoms, and two died.

Discussion

The success of cardiac surgery in modifying the devolutionary pattern of any stenotic valve lesion resulting from rheumatic activity depends upon the ability to alleviate the obstruction without unusual risk and without creating new and serious defects. The accomplishment is measured by comparing the clinical and physiologic manifestations of the disease before and after surgery against the background of their usual progress under conventional medical management.

Although an initial appraisal of transventricular commissurotomy [2] concluded that the technic relieved obstruction and granted clinical improvement to the large majority of patients who did not obtain equal benefit under carefully regulated medical routines, it also recognized a considerable operative risk, and the disturbing possibility of producing significant aortic regurgitation.

A comparison of the operative mortality of both methods reveals that the 10% risk of transaortic commissurotomy is a distinct improvement and compares favorably with the 8% death rate of mitral commissurotomy.[4]

A pertinent inquiry as to whether the decrease in mortality is attributable to operative technic or key issues in patient selection is most difficult because of the limited number of patients involved. For example, it is impractical to correlate the four deaths with age at the time of surgery, the presence of angina or congestive heart failure. Furthermore, in view of the varied functional classification of the patients who died, it is impossible to state whether the improved mortality rate was derived from better results in the ordinary patient, in the precariously ill, or in both.

However, it is helpful in clarifying the issue to underscore early trends, among which the incidence and circumstance of ventricular fibrillation are of great importance. Although the lethal arrhythmia occurred less frequently, perhaps because the anoxic myocardium was not traumatized, the hope that it could be eliminated by the transaortic approach as an independent and spontaneous cause of surgical death has not been realized. In surgery for aortic stenosis, ventricular fibrillation must be accepted as an unpredictable hazard, the frequency of which is determined only in part by the procedure employed.

The manner of death in one patient and the ultimate findings in two others who recovered testify to the possibility of dynamic, physiologically significant aortic regurgitation after transaortic commissurotomy. For the present, the actual incidence is quite similar to that observed with the transventricular route.

Peripheral pulse pressures and brachial artery tracings support the contention that the diastolic murmurs produced or exaggerated by the operation do not necessarily represent dynamic lesions. Thus, it is reasonable to claim that transaortic commissurotomy does not exchange one serious defect for

another. Conversely, a denial of the possibility of such an adverse result is an unrealistic view of established fact.

It is disappointing that a digitally controlled means of splitting aortic commissural fusion is not an absolute safeguard against the hazard of producing significant regurgitation. However, this is consistent with the experiences in mitral valve surgery and is a reflection of the many factors contributing to that complication, including the structural characteristics of the leaflets, the degree of calcification, and the skill and restraint of the surgeon.

Since all patients chosen for surgery had had prolonged experiences with medical management and a basic knowledge of the format of their disease, the postoperative improvement in dyspnea, fatigability, angina, syncope and vertigo which has been reported is important confirmation of the effectiveness of the surgical management of aortic stenosis. Particular note must be made of the consistency with which angina disappeared following operation.

The transaortic method has not extended the percentage of patients improved or the degree of their benefit. From this it may be concluded that this, or the transventricular procedure, successfully concluded, will result in equal success.

However, it is quite clear that not all of the patients obtained significant clinical relief. Indeed, in some instances operation was rewarded only by a continuing devolutionary state as ominous in its implications as the conditions dictating the surgical interference. When the error of creating a serious regurgitation is set aside, it is obvious that an important correlation exists between results, the morphology of the valve, and the ability of the surgeon to alter the size of the orifice.[5] In short, transaortic commissurotomy does not permit the surgeon to overcome all of the handicaps imposed by the structural abnormalities of the valve, among which extensive calcification and valvular thickening are most important. Although it remains true that the unyielding valve is technically more amenable to the direct transaortic approach, it is highly questionable whether in the majority of patients the improved effort is sufficient to turn the course of clinical events to a highly satisfactory result.

The most significant change in objective manifestations has been the decreased intensity of the rough systolic murmur, and the increased intensity of the second aortic sound developing in over one-half of the patients, and the specific alterations in the brachial artery tracings.

Although the auscultatory findings have not been correlated with valve areas, pressure gradients or clinical improvement, it is reasonable to accept them as indicative of more normal valve function and as important gains. In this area of results the transaortic equals but does not exceed the attainments of the transventricular operation.

In the past, the various anacrotic phenomena and the delay in the peak

of systole in brachial artery tracings have been linked to the presence and severity of aortic stenosis.[6] This requires reasonable qualification, because Goldberg [7] has shown that the position of the anacrotic notch is not determined exclusively by the degree of stenosis but is also influenced by pulse pressure and stroke volume. Certainly a critical, quantitative correlation has not been established between tracing contours and the valvular dynamics. At the present time an investigative program has been undertaken at the Cardiovascular and Pulmonary Research Laboratory of the Hahnemann Medical College and Hospital to clarify the problem but, for the moment, ample experimental and clinical evidence attests to the fact that aortic stenosis is characterized by a brachial artery tracing which varies sharply from the normal and includes variously placed interruptions in the upstroke or anacrotic limb and a constant delay in the peak of systole.

It is a logical deduction that the postoperative disappearance or modification of these abnormalities indicates a significant and beneficial alteration in the degree of aortic stenosis, even though the improvement cannot be estimated quantitatively. This view is strengthened by correlations which indicate that auscultatory and clinical improvement frequently is associated with these changes.

The experiences following transaortic commissurotomy are consistent with those reported after the transventricular approach, and lead to the conclusion that while both operations are capable of returning the brachial artery tracing to more normal patterns, neither is more consistently successful in that accomplishment.

There remain for discussion the serious question of mortality following successful conclusion of surgery and an examination of the causes of these deaths.

The death of any patient is an obvious indictment of treatment and represents either faulty concepts or implementation. If transaortic commissurotomy had produced a maximal increase in the size of the valve orifice in the two patients who subsequently died suddenly, the operation would have to be considered an inadequate therapeutic agent in the critical field of preventing acute death. However, both patients had diffusely calcified valves, and in neither was a satisfactory opening obtained. Therefore, although lethal pathophysiologic events may not be avoided by a transaortic commissurotomy, the issue appears to arise only when local conditions at the valve site hamper a reasonable technical effort. This fact qualifies the usefulness of transaortic commissurotomy but does not compromise its basic concept.

The unusual incidence of subacute bacterial endocarditis in this series of patients is contrary to all previous experience in aortic valve surgery and requires definitive explanation. Since the complication developed a short period after the operation in the majority of instances, the cause most logically rests with an important break in technic, inadequate antibiotic

protection,* or an unusual propensity of the mobilized aortic leaflets to nurture the growth of circulating bacteria.

The technic utilized for transaortic commissurotomy requires the use of the ungloved finger to preserve the delicate sensitivity of the bare digit for examination of the valve. Although a meticulous preoperative preparation of the hand was always practiced, and a positive skin culture was never obtained in a series of pilot surveys, the suspicion remains that the offending organisms may have been introduced into the circulation during the operative procedure. Adjustment of the antibiotic schedule has resulted, thus far, in the elimination of subacute bacterial endocarditis as a major problem in a large series of patients not included in this study.

Transaortic commissurotomy does not extend or alter the basic indications for the surgical treatment of aortic stenosis. It has been stated previously [2] that the primary indication for operative interference is a combination of subjective or objective manifestations of significant and progressive pathophysiology resulting from the disease, provided none of the contraindications is present.

When indications are outlined in such broad terms, further definition is required in order to apply basic concepts properly. Since dyspnea, angina, syncope, left ventricular enlargement, and the electrocardiographic pattern of left ventricular hypertrophy and "strain" represent expressions of significant, dynamic pathophysiology, patients with these findings clearly are candidates for operation. It is a reasonable contention that, within this clearly defined group, aortic commissurotomy is performed more safely and effectively when the clinical manifestations are recent rather than late.

A problem exists, however, with patients who are not symptomatic and who do not possess serious objective manifestations of their disease. Theoretically these individuals represent ideal candidates for operation from a risk standpoint. However, it is conceivable also that they may survive a full, unimpaired lifetime without surgery if the valve obstruction is adynamic and not progressive. A solution is envisioned when present investigative studies clarify the correlation between valve areas, gradients across the orifice, and blood flow with the onset and ultimate progress of the manifestations of aortic stenosis.

The contraindications to operation are rarely in dispute. In general, they include those anatomic and physiologic issues which prejudice immediate recovery or serve as known deterrents to the benefit expected from surgery. A primary contraindication is the presence of additional, significant incorrectable valve lesions, outstanding among which is aortic insufficiency. Congestive heart failure which does not respond to medical therapy, acute rheumatic activity, subacute bacterial endocarditis, and massive cardiac enlargement are absolute contraindications.

Although age and the functional status of the patient have a direct

* Superinfection in the presence of broad spectrum antibiotic therapy.

relation to the risk of surgery and its ultimate benefit, fixed criteria in either regard cannot be outlined.

For the present, the following scheme is suggested as an aid in the selection of patients:

Group I: Patients with the auscultatory findings of aortic stenosis but without the symptomatic or objective expressions of the disease. Left heart catheterization rarely shows a significant systolic pressure gradient across the aortic valve.

These individuals are not candidates for operation, since there is no present knowledge that the anatomic lesion invariably leads to important pathophysiologic developments.

Group II: Asymptomatic patients with left ventricular enlargement and/or left ventricular hypertrophy and "strain." Left heart catheterization usually reveals a significant systolic pressure gradient across the aortic valve.

Commissurotomy is indicated because of the presence of objective changes which presumably are progressive in nature.

Group III: Patients with either dyspnea, angina or syncope accompanied by left ventricular enlargement and/or left ventricular hypertrophy and "strain." Left heart catheterization usually reveals a significant systolic pressure gradient across the aortic valve.

Surgery is indicated because the clinical findings are manifestations of significant pathophysiology which presumably is progressive.

Group IV: Patients with advanced clinical manifestations of aortic stenosis and congestive heart failure. Left heart catheterization rarely shows a significant systolic pressure gradient across the aortic valve, because of diminished cardiac output and intrinsic myocardial disease.

Although operation may be performed, the risk is considerable and the accrued benefits may be minimal.

In any of the operable patients indicated, the following conditions take precedence and surgery is definitely contraindicated:

1. Significant incorrectable associated valve lesions.
2. Massive cardiac enlargement.
3. Acute rheumatic activity.
4. Subacute bacterial endocarditis.
5. Intractable congestive heart failure.
6. Serious complicating disease entities.

The material reviewed does not permit a final evaluation of transaortic commissurotomy. From these initial experiences, the operation has materially reduced the immediate mortality of the surgical treatment of aortic stenosis and offers the considerable advantage of a direct, intimate examination of the valve area and its acquired pathology. The technic does not eliminate or reduce the possibility of creating significant aortic regurgitation,

and its effectiveness is limited sharply by the morphology of the valve. In spite of these restrictions, transaortic commissurotomy is a striking therapeutic agent, entirely capable of modifying the clinical pattern and certain objective manifestations of dynamic aortic stenosis.

Conclusions

1. An evaluation of the surgical management of aortic stenosis by means of transaortic commissurotomy is described in which the mortality and complications are analyzed and the preoperative clinical and objective findings in 40 patients are compared with those three to 15 months after operation.

2. The operative mortality of aortic commissurotomy has been reduced to 10% by means of the transaortic approach.

3. The improvement noted in the key symptoms of fatigability, dyspnea, angina and syncope following transaortic commissurotomy is comparable to that obtained by the transventricular technic.

4. Symptomatic changes are accompanied by important alterations in the brachial artery tracings and auscultatory findings which suggest improvement in valve function.

5. Transaortic commissurotomy does not reduce the likelihood of producing dynamic aortic regurgitation.

6. The indications and contraindications for aortic commissurotomy are outlined.

Summario in Interlingua

Es presentate un analyse del tractamento chirurgic de stenosis aortic, effectuate in 40 patientes per medio del technica de commissurotomia transaortic. Le mortalitate operatori esseva 10 pro cento. Le causas de morte esseva connectite con le production de letal regurgitation aortic, le disveloppamento de fibrillation ventricular, e le formation de un embolismo cerebral. Le curso hospitalari postoperatori esseva libere de incidentes in le majoritate del casos, ben que complicationes cardiac sin mortalitate occurreva in 36 pro cento del superviventes. In le summario del resultatos final nos ha considerate solmente patientes qui esseva operate al minus tres menses antea. Iste gruppo includeva 27 individuos. Sex de illes esseva sub observation durante 12 menses o plus. Occurreva, in le gruppo, sex mortes retardate. In quatro de illos le causa immediate del morte esseva subacute endocarditis bacterial. Inter le patientes vive, 15 (71,4 pro cento) esseva classificate como "meliorate," quatro (19 pro cento) como "pejorate," e duo (9,5 pro cento) como "non alterate." Le melioration esseva le plus frappante in patientes in qui angina e syncope esseva le major molestias, ben que circa duo tertios exhibiva effectos benefic relative a lor principal symptomas de dyspnea, fatiga, e vertigine. In 11 casos (52,3 pro cento), le rauc aortic murmure sytolic esseva reducite in intensitate per le operation, e in 12 casos (57,1 pro cento) le secunde sono aortic deveniva plus distincte. Commissurotomia transaortic produceva le murmure de regurgitation aortic in un medietate del patientes in qui illo habeva essite absente ante le operation; illo reinfortiava le murmure de regurgitation aortic in un sexto del patientes in qui illo habeva essite presente. In tres casos, dynamic regurgitation aortic esseva producite. Nulle alterationes significative esseva

notate in electrocardiogramma o roentgenogramma. Alterationes del registration de pression brachio-arterial post commissurotomia aortic non reflecteva accuratemente le alterationes del stato clinic. Es presentate le indicationes pro commissurotomia transaortic. Illos include omne patientes in qui le obstruction del valvula aortic es considerate como dynamic e physiologicamente significative, providite que nulle del sequente contraindicationes es presente: (1) Associate lesiones valvular de character significativemente incorrigibile. (2) Massive allargamento cardiac. (3) Acute activitate rheumatic. (4) Subacute endocarditis bacterial. (5) Congestive disfallimento cardiac de character intractabile. E (6) serie complicationes per altere entitates morbose. Nos conclude que commissurotomia transaortic es un frappante technica therapeutic que es capace a modificar le stato clinic e certe manifestationes objective de dynamic stenosis aortic.

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COMPLICATIONS OF INFECTIOUS MONONUCLEOSIS *

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THERE has been interest in the last few years in the complications of infectious mononucleosis. Scattered reports of these complications have increased but, because examples are still quite unusual, they are accompanied by interest, uncertainty and even excitement at the bedside. It is the purpose of this paper, after a background introduction to infectious mononucleosis, to report an example of this illness accompanied by encephalitis and hemiplegia, and to review comprehensively the known existence and significance of the varied complications. A previous review was included in Bernstein's monograph on all phases of infectious mononucleosis in 1940.[1]

The earliest descriptions of the illness now known as infectious mononucleosis are credited to Filatoff [2] and Pfeiffer.[3] Filatoff described idiopathic adenitis in a Russian textbook of pediatrics in 1885, and Pfeiffer described drusenfieber, or glandular fever, in 1889. Pfeiffer mentioned cervical lymphadenopathy, fever and involvement of the spleen and the liver; he stressed that the leukopenia was not severe enough to be the primary cause of the disease. There followed a period of about 20 years in the medical literature in which there was confusion between this illness and leukemia.[4] In 1920 Sprunt and Evans [4] coined the term "infectious mononucleosis," and attempted to separate this group of relatively benign patients from those with lymphatic leukemia. In 1923 Downey [5] very carefully described and classified the white blood cells in infectious mononucleosis, and pointed out their differences from those of acute lymphatic leukemia. He described three types of atypical lymphocytes based strictly upon blood morphology and not related to the leukocyte count or to the severity of the disease. The blood cell morphology was again carefully considered by Baldridge, Rohner and Hansmann [6] in a general review published in 1926. There was little additional interest in this field until 1932, at which time Paul, of the Yale medical department, and his resident, Bunnell,[7] noted the high nonspecific or heterophil agglutination that serum from patients with infectious mononucleosis makes with the red blood cells of sheep. This discovery was made accidentally when these men were trying to utilize the Forssman group of antibodies clinically in rheumatic fever. Davidsohn [8, 9] later clearly demonstrated with his differential test that the infectious mononucleosis heterophil serum agglutination does not belong to the Forssman, or horse serum, sensitivity group. In recent years the flocculation liver

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function tests have also been used as an aid in differential diagnosis, following knowledge that some liver function impairment occurs in almost all cases.[10, 11]

The latest interest and attention have been in regard to the complications of this disease. It is now known [12, 13, 14] that the mononuclear and lymphatic infiltration may be seen in all organs of the body in the more severe forms of infectious mononucleosis. While the lymph nodes and spleen are usually involved in this process, it may also occur and become associated with symptoms in the liver, central nervous system, lungs, heart and kidneys. A case report follows in which the disease was ushered in with most severe neurologic signs and symptoms.

Case Report

An 18 year old boy was admitted in a semistuporous state to the Neurology Service of the State University of Iowa Hospitals on January 13, 1954. His mother stated that he sustained a football injury in September, 1953, and thereafter had mentioned a numbness of the right side of his face for two months. He received a second football injury in November and was said to have been unconscious for one hour; there were no known sequelae following this injury. He was also involved in minor automobile accidents in November and December, 1953. On January 5, 1954, he felt as if he were coming down with a cold. On January 8 he described a sensation of lightheadedness, and on subsequent days a weakness in the right leg and difficulty in enunciating. He slipped into a comalike state on January 11, 1954, and was admitted to the University Hospitals two days later.

The admission physical examination revealed an acutely ill boy with no signs of recent bruises or lacerations. He responded only to painful stimuli, and this response consisted of thrashing of his body. His right arm and leg were flaccid. The temperature was 104° F. The blood pressure was 120/70 mm. of Hg. The pulse was 90 per minute. The pupils were round and equal and reacted to light. The fundi appeared normal but the discs were slightly elevated, with blurred medial borders. There was no nuchal rigidity. There was mild generalized lymphadenopathy. There were no positive chest, cardiac or abdominal findings. Leg-raising tests were negative, and there was a relative hyperreflexia on the right side.

The following laboratory data were collected the day of admission: Hemoglobin, 14 gm. White blood count, 18,500. Urinalysis, negative. Cerebral spinal fluid, clear, with 130 mm. initial pressure, 128 lymphocytes, a negative Pandy reaction and 50 mg.% protein. Skull and chest films were normal.

The following day the patient's temperature dropped to 102° F. but he remained unresponsive. A horizontal nystagmus with quick component from right to left was noted bilaterally. The differential blood count disclosed 78% lymphocytes, with several atypical cells. Heterophil agglutination was positive, 1:512; the Davidsohn differential test was used.

On the sixth hospital day the patient was still running a low grade fever. He appeared somewhat more responsive and could move his right hand. The spleen was palpated this day for the first time. The ophthalmologists stated that the blurred discs probably did not represent papilledema. Agglutination reactions for brucellosis, mumps, East and West encephalitis, equine encephalitis and lymphocytic choriomeningitis were all negative.

On the ninth hospital day the patient appeared to be worse and was completely unresponsive. The heterophil titer was now 1:256. After discussion, the patient

was transferred to the neurosurgical department and ventriculograms were performed to rule out an intracranial mass. These were negative. The patient was returned to the neurology service and slowly improved with symptomatic and physical therapy.

By the sixteenth hospital day he appeared alert and could answer questions by nodding his head. He continued aphasic. His reflexes were hyperactive on the right side, and he held the right arm and leg in a flexion contracture. The latter was improving with physical therapy.

By the fortieth day his speech had returned and was normal. Function of the right side of the body had also returned, and he walked with only a slightly noticeable limp. He was discharged, and at the time of his last return check-up, on April 6, 1955, he was considered normal except for slight persistent increased reflexes on the right side of his body.

It would appear justifiable to review the literature and to stress the complications of infectious mononucleosis in view of the repeated difficulty in diagnosis and lack of assurance in management which almost always follow their occurrence.

Neurologic Complications

At least 64 cases with severe neurologic complications have now been reported.[15-63] The first cases were reported independently by Johansen [15] and by Epstein and Dameshek.[25] The frequency of reports is accelerating. In order to group the complications in numbers, the classification of Bernstein and Wolff [32] is helpful. This includes the following groups:

1. *Serous meningitis.*[15-17] The patient has headache, nuchal rigidity and increased spinal fluid pressure. There is usually no spinal fluid pleocytosis or increased protein. This type is probably fairly common, but only four acceptable cases were reported.

2. *Meningitis.*[16, 18-24] The patient has headache, nuchal rigidity and increased spinal fluid pressure. In addition, he will have a positive leg-raising test, spinal fluid cells and usually increased protein. Ten reports of this type of case were found.

3. *Meningo-encephalitis.*[25-27] The above symptoms and signs are present, plus symptoms and signs of encephalitis such as severe lethargy, dizziness, staggering, nystagmus, aphasia, ataxia, coma and hemiplegia.

4. *Encephalitis.*[8, 28-46] The primary symptoms and signs of this group are only of encephalitis. The bibliography includes 20 cases.

5. *Acute Polyneuritis or Guillain-Barré Syndrome.*[22, 30, 43, 47-59] The patient has weakness, flaccid paralysis and increased protein, with or without spinal fluid pleocytosis. There are 18 reported cases, with four deaths.

6. *Peripheral Neuropathy.*[18, 43, 60-63] Infectious mononucleosis findings are complicated by sudden pain and paralysis of a muscle or group of muscles. The spinal fluid, when examined, has been normal.

In reading through the reports of these complications, one is again impressed with the extreme difficulty in diagnosis. Diagnosis was often made accidentally, as in our case, by the blood morphology. The problem is even

more difficult when the lymphadenopathy is slight and when the neurologic signs precede all other signs in time sequence. This case report appears typical for the encephalitic group inasmuch as there was complete recovery in spite of a stormy course. The neuritis group, however, includes four deaths in 18 cases. Also, the six cases reported by Thomsen and Vimtrump,[64] not usually included in lists because of incomplete data, probably also fall into the Guillain-Barré classification. Of interest, especially in the encephalitic group, are dramatic signs and symptoms usually denoting other serious illness. Grand mal seizures were described five times,[32, 33, 37, 40, 43] and coma, or unresponsive mental status, has now been reported all of 13 times, including our case.[8, 26, 32, 33, 37, 39, 40, 43, 44, 45, 46, 58] The recent report by Kalmansohn [45] pertained in particular to this problem. Cheyne-Stokes respirations were reported three times,[33, 40, 46] and hemiplegia has been noted upon three occasions before this report.[26, 40] Papilledema was noted by Piel [59] and Karpinski.[44] Residual damage other than death was observed by Slade,[30] Nixon [55] and Saksena.[62] The problem of therapy has not been settled. Bonynge [41] and Creaturo [53] used 2–3 dimercaptopropanol (BAL) with what they believed were promising results, and Hubler [33] and Fiese [57] used ACTH and cortisone, with perhaps beneficial results. However, there is no question but that intensive physiotherapy is of help during the convalescent period.

The relationship between infectious mononucleosis and the neuritis often listed in the bibliography as the Guillain-Barré syndrome has been clarified by the work published in 1949 by Haymaker and Kernohan.[65] Landry in 1859 described a neuropathy of unknown origin in 10 patients, with two deaths.[66] Although Landry described several variants of this disease process, the ascending paralysis with poor prognosis commonly connoted with his name refers to a motor neuropathy, starting with the legs and working upward in a systematic, progressive fashion.

Guillain, Barré and Strohl in 1916 reported two nonfatal cases with similar symptoms.[67] Their report gained recognition because they examined the spinal fluid and emphasized a dissociation between the high spinal fluid protein and the absence of spinal fluid pleocytosis. In 1936 Guillain [68] published 10 additional cases of what was now termed the Guillain-Barré syndrome, and again emphasized the above dissociation, the excellent prognosis of his group, the frequent accompanying sensory changes with the motor paralysis, and the lack of significant fever or meningeal signs. Haymaker and Kernohan favored the term Landry-Guillain-Barré to denote this group of illnesses; they stated that one should think of the two types as opposite ends of one continuum representing a single disease process. They pointed out that there has been no evidence that the high spinal fluid protein correlates with the prognosis. They state that pathologically the damage occurs in the spinal ganglion of the peripheral nervous system where the anterior and posterior roots fuse. In the cases where the motor nuclei of

the brain stem and the anterior horn cells are injured, it is believed to be a secondary retrograde process. Infectious mononucleosis has been reported as the cause of this process in 18 cases. It is, however, believed to be responsible for only a small fraction of all cases.

Rupture of the Spleen

Spontaneous, or nearly spontaneous, splenic rupture is a complication now recorded in the literature in at least 21 patients, with seven deaths.[69-81, 27] Smith and Custer [77] state that in the files of the Army Institute of Pathology, of the 44 cases coded as "Spleen, Spontaneous Rupture," infectious mononucleosis stood second as a cause in seven, exceeded only by recurrent malaria in 22. The capsule and trabeculae of the spleen become weakened and sometimes literally dissolved by the "infiltration" of lymphocytes and large mononuclear cells, so that such minor trauma as palpation in physical examination, getting into bed or defecation may allow the spleen to rupture and produce peritonitis. In most cases it is believed that the rupture is preceded by hemorrhage into the subcapsule, with gradual stripping of the capsule.[76, 77] Diagnosis after rupture is sometimes hindered by a shift in the differential blood count to the left, which occurs when the reaction of peritonitis stimulates a normal bone marrow. Diagnosis is made by knowledge of this possible complication in infectious mononucleosis and by signs of shock and abdominal fluid. Rapid surgical treatment, with removal of the spleen and supportive transfusions, is essential for recovery.

Hepatitis

The literature now consistently states that some hepatitis is involved in nearly all cases of infectious mononucleosis.[82-84, 10, 11] Jaundice occurred in 6.6% in one recent series;[85] this is now definitely believed a result of hepatocellular damage, rather than compression of drainage mechanically from the enlarged glands. Leibowitz [11] reviewed this subject and reported a case of infectious mononucleosis with hepatitis, followed for a period of three years, which became cirrhosis of the liver; there was also an alcoholic history in this case. The inference appears to be that infectious mononucleosis may occasionally contribute to the pathogenesis of cirrhosis of the liver, just as infectious hepatitis is believed to do.

Anemia

A factor stressed over the years with regard to problems of diagnosis has been the clinical absence of anemia and thrombocytopenia in infectious mononucleosis when contrasted with acute leukemia. Yet there have now been at least 16 case reports of a hemolytic type of anemia occurring at the height of the infectious mononucleosis illness.[86-99] The difficulty in diag-

nosis is again stressed in these cases. The theoretic explanation for the anemia in these cases is that the large spleen begins to form autohemolysins and auto-agglutinins which react with the patient's red blood cells with hemolysis and anemia.[86, 87] The Coombs' test or the demonstration of the reaction of antibodies with red blood cells has been reported positive in four cases [93, 95, 98, 99] and negative once.[96] The relationship of positive cold agglutinins [97] and Donath-Landsteiner reactions [95] certainly is not clear. The realization that acute hemolytic anemia may occur and will probably disappear with the fall in heterophil agglutination antibody titer will probably make consideration of a splenectomy unnecessary in these patients,[96] although splenectomy has been reported once.[91] ACTH was used with possible favorable clinical results in three reported cases [93, 96, 99] and cortisone in one.[99]

Thrombocytopenic Purpura

It has long been recognized that a mild bleeding tendency, characterized by mild epistaxis, petechiae, ecchymosis and hematuria, is not uncommonly found during the illness due to infectious mononucleosis.[1, 100] However, a true hemorrhagic diathesis or thrombocytopenic purpura is rare; this phenomenon has however now been reported 16 times.[101-113] Laboratory tests usually showed very low platelet counts, prolonged bleeding time and poor clot retraction. There was no initial anemia, and any anemia is due to blood loss. The complication comes explosively and during the height of the illness, and is characterized by favorable response to transfusions and ultimate recovery. No deaths have been reported. There have been no case reports evaluating ACTH or cortisone therapy.

Pulmonary Complications

Pulmonary complications were reviewed in 1954 by Vander; [114] he added the first reported case of infectious mononucleosis with pleural effusion. Bronchopneumonia and pneumonia have been previously described, and Wechsler [115] reported that in one Army epidemic pulmonary infiltration was found in 2% of the cases. The x-ray and clinical picture were similar to those in atypical pneumonia. The accompanying cough is said to simulate pertussis.

Cardiac Complications

Cardiac complications have not been stressed, and the reviews indicate that the cardiac complications are usually subclinical and benign, and are manifested by transient nonspecific electrocardiographic alterations.[116] Autopsy confirmation of myocarditis [12, 117] shows the basic lesion to be a perivascular infiltration of normal and abnormal lymphocytes. The latest reviews and case reports deal with acute pericarditis.[116, 118, 119, 120] There have now been nine case reports of clinical pericarditis in conjunction with

infectious mononucleosis. The four reported [116, 118] were in the 17 to 26 year age group, and all had severe chest pain, pericardial friction rubs and electrocardiographic confirmation, with elevated RS-T segments and inverted T waves. Thus there appears to be at least one known cause for the acute nonspecific or idiopathic pericarditis.

Abdominal Complications

During the acute stages the mesenteric lymph nodes may produce nausea, vomiting, right lower quadrant pain and abdominal rigidity. This has been mistaken for appendicitis, and commonly the only indication of the real diagnosis is found in the differential count.[1, 29]

Kidney

Tidy [100] reported an epidemic in which hematuria was found in 6% of cases; it may be the first symptom. Custer and Smith [12] found the lymphocytes confined to the periphery of vessels, and also found aggregates in the interstices of the cortex. Abnormal constituents in the urine are red and white blood cells and, less often, albumin and casts.[1, 23] There is no known relationship between the transient nephritis and chronic kidney disease.

Eye Manifestations

A comprehensive review of the eye manifestations of infectious mononucleosis, plus a case report of a 17 year old girl with papilledema and infectious mononucleosis but without neurologic manifestation, was published by Tanner in 1954.[121] He states that oculomotor palsies have been reported as the most frequent eye complication, as in the reports of Sucker,[26] Vaughn [27] and Fledelius.[60] Papilledema associated with the neurologic manifestation had been previously reported at least four times,[18, 41, 44, 59] and additional reports of papilledema without known neurologic symptoms and signs by Karpe,[122] Ashworth [123] and Blaustein.[124] A dry granular conjunctivitis may appear early in the disease; it is often unilateral and most commonly on the left side.[121] The palpebral conjunctiva may be fiery red, with discrete, punctate, whitish follicles.

Skin Manifestations

Discussion of the skin manifestations is included in reports by Bernstein,[1] Wechsler [28] and Stevens.[85] Any type of rash may occur, but the type, or its severity, does not appear to have any correlation with the severity of the illness. A rash was noted in 7.6% in a study of 210 sporadic cases.[85] Types noted included macular, maculopapular, urticarial, erythema multiforme, morbilliform, hemorrhagic and nodular.

Summary

The complications of infectious mononucleosis are closely associated with lymphocytic and mononuclear cell infiltration into the various organs and tissues of the body. This report contains a review of complications involving the neurologic system, spleen, liver, lungs, heart, mesenteric lymph nodes, kidney, eye and skin. A discussion of infectious mononucleosis accompanied by severe anemia or thrombocytopenic purpura is included. Also presented is a case report of a young man with infectious mononucleosis complicated by encephalitis, including coma and hemiplegia; in this case there was essentially complete recovery. Attention is thus drawn to the varied forms that the illness may take and the many times it must be included in a differential diagnosis.

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Summario in Interlingua

Recente annos ha vidite un augmento del interesse in le complicationes de mononucleosis infectiose, proque iste complicationes—quando illos es serie—es quasi semper accompaniate per indecision diagnostic e ergo per incertitude in re le melior maneamento del patiente. Le objectivo del presente articulo es passar in revista de maniera comprehensive le cognoscite existentia e signification del varie complicationes e reportar un exemplo de mononucleosis infectiose associate con encephalitis, hemiplegia, e coma. Le patiente in question attingeva un practicamente complete recuperation con le uso de un therapia supportative.

Nos opina que le complicationes de mononucleosis infectiose es le resultato del infiltration de cellulas lymphocytic e mononuclear a in le organos e histos del corpore. Nos ha passate in revista le effectos del infiltration in le systema nervose central, splen, hepate, pulmones, corde, nodos lymphatic mesenteric, renes, oculos, e pelle. Es includite un discussion del morbo accompaniate per sever anemia o purpura thrombocytopenic.

Usque nunc al minus 64 casos con complicationes neurologic ha essite reportate. On debe prestar attention a encephalitis que pote includer serie signos del typo de titubation, ataxia, respiration de Cheyne-Stokes, e aphasia, como etiam hemiplegia e coma. Acute polyneuritis o le syndrome de Guillain-Barré pote disveloppar se, insimul con debilitate, paralyse flaccide, e augmento del proteina in le fluido spinal. Le casos reportate de iste complication include quatro casos mortal.

Le plus commun causa de morte in mononucleosis infectiose reportate in le litteratura es sanguination ab un ruptura del splen allargate. Ruptura spontanee (o quasi spontanee) del splen es reportate in le litteratura pro 21 patientes. Septe de iste casos esseva mortal. Ictero ab lesiones hepatocellular occurre in un parve procentage de casos e evoca un diagnose differential de ictero. Mononucleosis infectiose es etiam un causa del non-specific o idiopathic pericarditis. Le nodos lymphatic mesenteric pote allargar se, causar dolor, e simular appendicitis con alte grados de verosimilitude. Contos differential es communmente le sol indication del diagnose correcte. Omne genere de eruption cutanee pote accompaniar le infection. Le typo e le severitate del eruption non es correlationate con le curso o le grado de severitate del morbo.

Le supra-presentate exemplos illustra un certe numero del plus importante variationes del morbo e indica in qual grande numero de casos le presentia de mononucleosis infectiose debe esser prendite in consideration in le diagnose differential.

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OBSERVATIONS ON THE INDIVIDUAL EFFECTS OF SMOKING ON THE BLOOD PRESSURE, HEART RATE, STROKE VOLUME AND CARDIAC OUTPUT OF HEALTHY YOUNG ADULTS * †

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INTRODUCTION

THERE is increasing evidence that smokers suffer from coronary artery disease somewhat more frequently than nonsmokers.[1-4] The reason for such an association is not known. English, Willius and Berkson first demonstrated the statistical validity of this finding in 1940, when they compared the records of 1,000 smokers and 1,000 nonsmokers and found a significantly higher incidence of coronary artery disease among smokers 40 to 59 years old than among nonsmokers of comparable age.[1] The authors expressed the belief that "in all probability the smoking of tobacco was not an etiologic factor but was perhaps an influence that affected the course and the progress of the disease." In discussing their paper, Dr. Soma Weiss stated the view of those who doubt even that conjecture when he said, "All one can say is that smoking was more prevalent, but the interpretation of this finding is difficult. For example, one may give the interpretation that the temperament of the hard-working individual who is predisposed to coronary artery disease would make him the type of individual who would also smoke, but the fact that he is smoking does not justify a conclusion that the smoking per se is a causative or even a contributory agent of coronary disease." Recently, a similar controversy has arisen over the relationship of cigarette smoking to lung cancer. As a by-product of the extensive statistical surveys carried out by the American Cancer Society and by the British Medical Research Council in that regard, reports of excessive deaths from coronary artery disease among white male cigarette smokers in contrast to such deaths among nonsmokers have once more brought the problem of the relationship of smoking to heart disease into prominence.[3, 4] If deleterious effects from smoking actually exist, it seems clear that there is a

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marked variation in individual susceptibility to the noxious influence, since the majority of habitual smokers do not succumb prematurely to coronary artery disease.

While individual variations in the effects of smoking upon the circulation of normal subjects have been noted in the past, the possible significance of such diversity has not been systematically studied.[5-10] Little attention has been paid to the possibility that the varying reactions of healthy young adults to smoking are expressions of basic differences in the physiology of the individual which are important in terms of future health or cardiovascular disease. Accordingly, we are investigating the circulatory effects of smoking in a group of Johns Hopkins medical students as a part of a long-term research project concerning the hereditary, physiologic and psychologic precursors of hypertension and/or coronary artery disease.[11-14] It is our ultimate purpose to discover whether the circulatory response to smoking is of predictive value in regard to the later development of coronary artery disease or hypertension in a given individual.

All smoking tests were performed on a ballistocardiograph, so that stroke volume and cardiac output could be studied in conjunction with blood pressure and heart rate. Interest in the smoking test has recently been stimulated by the discovery that, after smoking, the ballistocardiograms of patients with coronary artery disease show deterioration of form much more frequently than do tracings from normal subjects of similar age.[15-17] Gross changes in the ballistic records of many coronary patients and of some normal subjects over 30 years of age make it impossible to measure and compare the over-all changes in stroke volume and cardiac output which occur in these groups after smoking. The preservation of good ballistic form after smoking which is consistently found in healthy young adults, on the other hand, presents an excellent opportunity for such quantitative measurements of the effect of smoking.[18-22] Accordingly, the present paper is concerned with a descriptive analysis of the cardiovascular changes which follow smoking as they are simultaneously reflected in each of seven variables: (1) systolic pressure; (2) diastolic pressure; (3) pulse pressure; (4) heart rate; (5) stroke volume; (6) cardiac output, and (7) cardiac index. Detailed analysis of variations in electrocardiographic and ballistocardiographic wave forms is not given in this report. It may be stated that no major changes were encountered.

Method

The smoking tests were carried out on 113 medical students, 103 men and 10 women, who were 21 to 35 years of age, with a mean age of 25 years three months; only five subjects were over the age of 28 years. All were in good general health; none had organic heart disease or hypertension. Of the group, 82 were smokers and 31 were nonsmokers. The tests were performed under "casual" rather than "basal" conditions, in spare time during

the academic day. The subjects were all in the postprandial state; with few exceptions, from one to three hours had elapsed since the previous meal. The subjects had not smoked for at least half an hour before the test.

After being weighed and measured, the subject lay on the ballistocardiographic table with feet in good contact with the footboard. Successive blood pressure and pulse rates were obtained at minute intervals until stable (within 4 mm. of mercury or 4 beats per minute). A control ballistocardiogram with calibration and Leads I, II and III of the electrocardiogram were recorded. The subject was then given the first cigarette of a standard brand to smoke at his own pace, inhaling if possible. When two thirds of the cigarette had been smoked, another blood pressure was taken; the subject then took two more puffs and a ballistocardiogram and electrocardiogram were recorded. A second cigarette was smoked in similar fashion and the various measurements were repeated as before. Casual conversation was permitted early in the control and smoking periods, but the subject remained quiet for several minutes before the experimental measurements were taken.

The ballistocardiograms were taken on a Starr-type bed with a platform frequency of eight cycles per second, and recorded on a Sanborn Viso-Cardiette. The first 37 tests were recorded on a single channel instrument, the rest on a Twin-Viso-Cardiette, the ballistocardiogram and electrocardiogram being simultaneously recorded. The heart rate per minute was calculated to the nearest 0.1 beat from the number of systolic waves in a 20 second period. Two pairs of large and two pairs of small I and J waves were measured in each of the control and postsmoking tracings; amplitude was measured in millimeters and duration in .01 second. From these data the area of each wave was computed, the mean area of a pair of large and a pair of small I waves and J waves was found and corrected according to the calibration factor. The stroke volume was calculated according to Tanner's formula, $\sqrt{2I - J\ (\sqrt{c})} \times 100$, where I and J represent the mean corrected areas for the corresponding waves, and c is a constant.[28] The cardiac output was obtained by multiplying the stroke volume by the heart rate per minute. To obtain the cardiac index, the cardiac output expressed in liters per minute was divided by the surface area computed from the height and weight of the subject according to the Dubois nomogram. Thus the four basic measurements of systolic pressure, diastolic pressure, heart rate and stroke volume were expanded by means of combinations and transformations to yield three additional measurements, as follows:

1. Pulse Pressure = (systolic pressure) — (diastolic pressure)
2. Cardiac Output = (heart rate) × (stroke volume)
3. Cardiac Index = (cardiac output) ÷ f(height, weight), where f(height, weight) is an estimate of the surface area of the subject as given by a standard formula.

TABLE 1

Summary of Cardiovascular Changes after Smoking in All Subjects

	Measurement	Mean	Range		S.E. of Mean	S.D.	t
			High	Low			
Control value N = 113	Systolic pressure	114.5	158	92	0.98	10.47	
	Diastolic pressure	71.9	94	54	0.65	6.86	
	Pulse pressure	42.6	70	24	0.88	9.39	
	Heart rate	69.6	94	38	1.01	10.74	
	Stroke volume	107.6	144.0	62.3	1.55	16.52	
	Cardiac output	7,413.	10,850.	4,740.	116.	1,234.	
	Cardiac index	3.82	5.77	2.48	0.060	0.634	
Absolute change from control value after first cigarette N = 113	Systolic pressure	+2.9	+22	−10	0.53	5.67	5.45**
	Diastolic pressure	+4.6	+16	−6	0.48	5.10	9.62**
	Pulse pressure	−1.7	+14	−22	0.61	6.57	2.84*
	Heart rate	+6.6	+39	−7	0.71	7.58	9.27**
	Stroke volume	−4.0	+12.0	−25.0	0.68	7.23	5.82**
	Cardiac output	+373.	+3,030.	−960	62.2	660.8	6.00**
	Cardiac index	+0.19	+1.64	−.52	0.032	0.337	6.00**
Absolute change from value after first cigarette, after second cigarette N = 110	Systolic pressure	−0.5	+8	−10	0.39	4.06	1.36
	Diastolic pressure	−0.2	+12	−12	0.41	4.28	.56
	Pulse pressure	−0.3	+14	−16	0.49	5.13	.59
	Heart rate	+0.3	+11	−29	0.58	4.91	.59
	Stroke volume	−1.1	+29.0	−44.0	0.85	8.93	1.27
	Cardiac output	−29.	+2,880.	−3,500.	65.7	688.6	.44
	Cardiac index	−0.01	+1.30	−1.40	0.032	0.335	.28

Statistical significance: * = $p < 0.1$; ** = $p < .001$.

For purposes of analysis, then, the following are under consideration:

1. Resting levels of systolic pressure, diastolic pressure, pulse pressure, heart rate, stroke volume, cardiac output and cardiac index.
2. The *change* observed in each of these following the smoking of one cigarette.
3. The *further change* observed following the smoking of the second cigarette.

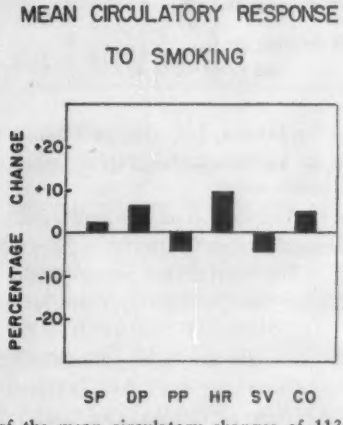

FIG. 1. The pattern of the mean circulatory changes of 113 healthy young adults in response to smoking one cigarette.

SP = systolic pressure DP = diastolic pressure PP = pulse pressure
HR = heart rate SV = stroke volume CO = cardiac output

In figures 1 through 4 cardiac index is not shown, since the *percentage changes* in cardiac output and cardiac index are necessarily identical.

Results

A. *General Effects:* The changes following smoking as observed in the entire group are summarized in table 1 and figure 1. On the average, systolic pressure, diastolic pressure, heart rate, cardiac output and cardiac index increased, while pulse pressure narrowed and stroke volume diminished. The effects were most striking after the first cigarette, and were statistically significant. The second cigarette produced negligible additional changes. The direction and degree of change after smoking varied greatly from subject to subject, so that the range of values for each circulatory determinant following smoking was very wide. Lack of uniformity in the *direction* of change was found not only in regard to blood pressure and heart

Table 2

Direction of Circulatory Changes Immediately after Smoking

	Systolic Pressure	Diastolic Pressure	Pulse Pressure	Heart Rate	Stroke Volume	Cardiac Output
A. After first cigarette N = 113						
Percentage of subjects showing increase	61.9	71.7	34.5	82.3	28.3	73.5
Percentage of subjects showing no change	15.0	15.0	9.7	1.8	3.5	0.0
Percentage of subjects showing decrease	23.0	13.3	55.8	15.9	68.1	26.5
B. After second cigarette N = 110						
Percentage of subjects showing increase	60.0	75.5	26.4	79.1	28.2	72.7
Percentage of subjects showing no change	11.8	13.6	17.3	1.8	1.8	0.0
Percentage of subjects showing decrease	28.2	10.9	56.4	19.1	70.0	27.3

rate, as has been noted by others, but also in respect to stroke volume and cardiac output revealed by ballistocardiographic measurements, as shown in table 2.

B. *Individual Effects:* Inspection of the individual responses to smoking reveals a variety of hemodynamic patterns. Several distinctive ones are illustrated in figure 2. The variations found make it apparent that the smoking stimulus may alter the circulatory equilibrium in a number of *different* ways.

In order to understand better the basic interrelationships shown by these patterns, the individuals presenting the most extreme changes of each kind after smoking a single cigarette were identified, and 12 groups of 10 subjects each were formed: those with the greatest percentage *increase* and those with the greatest percentage *decrease* in systolic pressure, diastolic pressure,

pulse pressure, heart rate, stroke volume and cardiac output, respectively. The mean circulatory changes for each group are given in figure 3. From the appearance of these patterns, it is clear that not only single subjects but also groups of individuals have surprisingly different reactions to smoking, and that where selection of subjects is based on a unidirectional change of a single circulatory determinant, the other determinants also show characteristic alterations in behavior rather than varying at random. Out of the

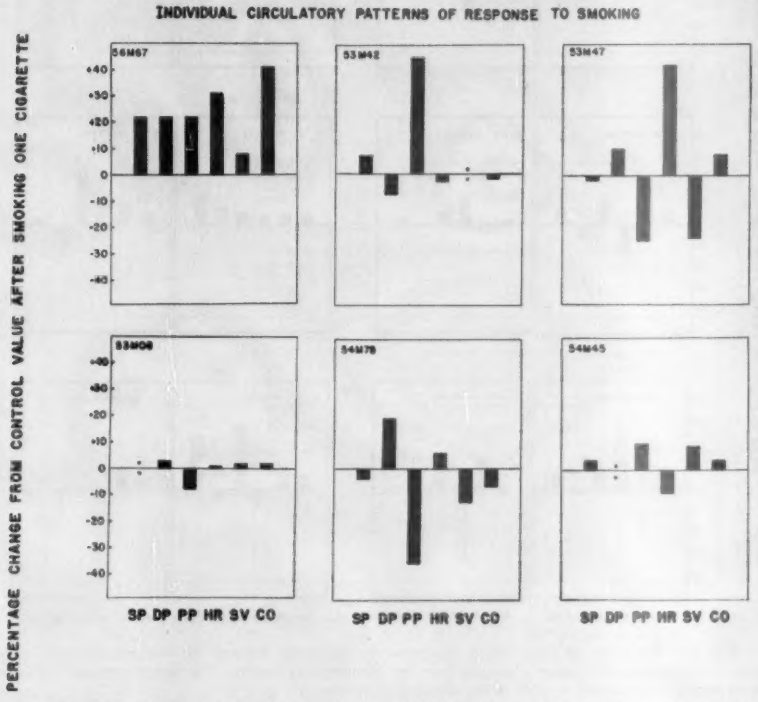

FIG. 2. Six different individual patterns of circulatory response to smoking. Each pattern represents the percentage changes in six variables shown by a single subject immediately after smoking one cigarette compared with his own control values. (Key as in figure 1.)

12 patterns in figure 3, only C, G, J and K show directional changes resembling the mean pattern for the total population (table 1, figure 1).*

What is the significance of these different patterns? Are they correlated with distinctive characteristics of the subjects themselves? In order to answer these questions, the findings were analyzed by dividing the population into groups according to sex, weight, smoking habits or parental history of

* Of the 113 individuals, 68 subjects exhibited one or more extreme changes after smoking. Fifty-five persons showed them in one or two determinants, while only 13 showed such changes in three to six variables.

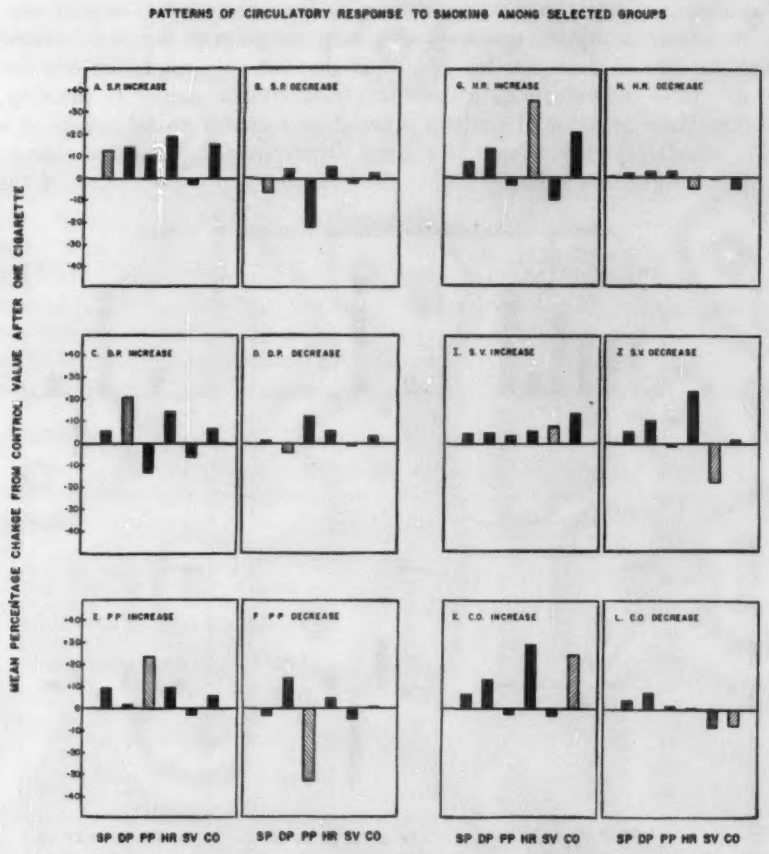
PATTERNS OF CIRCULATORY RESPONSE TO SMOKING AMONG SELECTED GROUPS
MEAN PERCENTAGE CHANGE FROM CONTROL VALUE AFTER ONE CIGARETTE
A. S.P. INCREASE
B. S.P. DECREASE
G. H.R. INCREASE
H. H.R. DECREASE
C. D.P. INCREASE
D. D.P. DECREASE
I. S.V. INCREASE
J. S.V. DECREASE
E. P.P. INCREASE
F. P.P. DECREASE
K. C.O. INCREASE
L. C.O. DECREASE
SP DP PP HR SV CO
SP DP PP HR SV CO
SP DP PP HR SV CO
SP DP PP HR SV CO

FIG. 3. Patterns of circulatory response to smoking among 12 selected groups. Each pattern represents the mean changes for the 10 subjects having the most extreme unidirectional change in regard to the index determinant.

▨ = index determinant

■ = associated determinants

hypertension and/or coronary artery disease. As is shown in table 3, the mean ages of the various groups were almost identical.

1. Sex: Compared with the men, the 10 women showed not only a more rapid resting heart rate but also a greater rise in heart rate and systolic pressure after smoking (table 3). Their stroke volume decreased simultaneously to a greater extent, however, so that changes in cardiac index of men and women after smoking were very similar.

2. Body Weight: The subjects were divided into three categories by

TABLE 3

Mean Cardiovascular Changes when Subjects Are Grouped According to Sex, Smoking Habits or Parental History

	Measurement	Sex		Weight			Smoking Habits		Parental History[5]			
		Men	Women	Over	Normal	Under	Non-smokers	Smokers	H − C −	H + C −	H − C +	H + C +
Number of subjects		103[1]	10	44	44	25	31	82[2]	49[3]	12[4]	11	9
Mean age in years		24.8	25.1	25.4	24.8	24.4	24.7	24.9	24.5	24.3	25.4	26.8
Control value	Systolic pressure	115.0	108.8	114.7	114.8	113.2	118.1	113.1	112.9	115.2	116.5	116.8
	Diastolic pressure	71.8	72.6	73.2	71.1	70.8	73.1	71.5	70.5	74.7	72.9	73.8
	Pulse pressure	43.2	36.2	41.5	43.7	42.4	45.0	41.6	42.4	40.5	43.6	43.0
	Heart rate	68.7	78.3	69.6	68.2	71.7	66.0	70.9	68.7	72.3	74.8	72.1
	Stroke volume	109.6	87.1	107.8	109.8	103.4	107.3	107.8	107.6	109.2	95.6	110.1
	Cardiac output	7,471.	6,821.	7,418.	7,434.	7,368.	7,076.	7,541.	7,321.	7,870.	6,973.	7,843.
	Cardiac index	3.81	3.90	3.64	3.89	3.99	3.65	3.89	3.81	3.94	3.65	3.89
Absolute change from control value after first cigarette	Systolic pressure	+2.6	+6.4	+2.7	+3.4	+2.3	+2.7	+3.0	+2.0	+6.1	0.0	+2.8
	Diastolic pressure	+4.7	+4.4	+4.3	+4.5	+5.3	+4.4	+4.7	+4.5	+6.6	+3.3	+4.4
	Pulse pressure	−2.1	+2.0	−1.6	−1.1	−3.0	−1.7	−1.7	−2.5	−0.5	−3.2	−1.7
	Heart rate	+6.3	+10.1	+6.7	+5.7	+8.1	+3.8	+7.7	+7.3	+8.3	+5.4	+6.5
	Stroke volume	−4.1	−4.5	−3.3	−4.9	−4.2	−3.1	−4.6	−3.9	+1.1	−5.9	−6.3
	Cardiac output	+343	+419	+415	+300	+436	+148	+461	+399	+992	+117	+262
	Cardiac index	+0.22	+0.26	+0.20	+0.16	+0.23	+0.07	+0.24	+0.21	+0.51	+0.06	+0.13
Absolute change from value after first cigarette, after second cigarette	Systolic pressure	−0.2	−2.5	−1.3	0.0	+0.5	−0.4	−0.5	−0.6	−5.0	+0.5	−0.7
	Diastolic pressure	−0.3	+1.4	−0.2	+0.3	−0.7	−0.4	−0.1	0.0	−3.7	+0.3	+0.9
	Pulse pressure	+0.1	−3.9	−1.1	−0.3	+1.2	0.0	−0.4	−0.5	+0.6	+0.1	−1.5
	Heart rate	−0.1	+2.2	+0.3	−0.2	+0.6	−0.6	−3.5	+0.3	+1.0	+1.7	−0.9
	Stroke volume	−0.5	−1.8	−2.9	+0.3	+1.1	−0.1	−0.9	−1.7	−2.0	+2.4	−3.0
	Cardiac output	−4	+13	−153	−39	+171	−47	−26	−53	−183	+287	−320
	Cardiac index	−0.05	0.00	+0.3	−0.1	+ .08	−0.01	−0.01	−0.02	−0.11	+0.16	−0.16

[1] = 100 after second cigarette. [2] = 79 after second cigarette. [3] = 47 after second cigarette. [4] = 11 after second cigarette.
[5] H = hypertension, C = coronary artery disease, + = definitely present in at least one parent, − = definitely absent in both parents.

comparing the individual's weight with the average for a given height, age and sex, as follows:

Overweight = 10 pounds or more above average weight
Normal weight = within + 9 to — 10 pounds of average weight
Underweight = more than 10 pounds below average weight

As is shown in table 3, the mean circulatory responses to smoking of these three groups of subjects were very similar. Accordingly, detailed statistical analysis of this comparison has been omitted in Section C.

3. Smoking Habits: Of the 113 subjects studied, 82 were smokers and 31 were nonsmokers. Immediately after smoking, the heart rate, cardiac output and cardiac index increased somewhat more in the smokers than in the nonsmokers (table 3 and figure 4). The subjects were further subdivided according to their specific smoking habits, as follows:

Class		N
I. Nonsmokers		31
II. Light smokers		26
A. Cigarettes (less than 10 a day)	17	
B. Pipes (less than 4 a day)	9	
III. Regular or heavy smokers		56
A. Cigarettes (10 or more a day)	48	
B. Pipes (4 or more a day)	4	
C. Mixed (combinations of cigarettes, cigars and pipes daily)	4	
Total		113

When the mean values for the 21 measurements for the various subgroups of smokers were compared, there was so little apparent distinction between them that they are not included in table 3.

4. Parental History: To ascertain whether adverse heritage influences the physiologic response to smoking, subjects were divided into four groups according to parental history. The presence or absence of hypertension and of coronary artery disease was determined in regard to the parents of each subject according to the method and definitions previously published.[14] Subjects were not included in this part of the analysis if the parental history was questionable or unknown in respect to either hypertension or coronary artery disease. It will be seen that where a history of hypertension alone existed, the increase of systolic and diastolic pressure, heart rate and cardiac output after smoking was exaggerated, and the stroke volume did not decrease (table 3 and figure 5). The response of subjects with a parent affected with coronary artery disease alone, on the other hand, showed practically no change in systolic pressure, a marked *decrease* in stroke volume, and very little rise in cardiac output. The pattern of subjects with

CIRCULATORY RESPONSE OF SMOKERS VERSUS NONSMOKERS

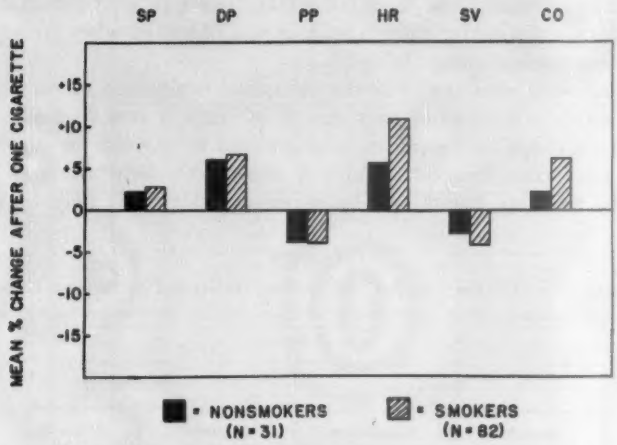

FIG. 4. The patterns of circulatory response to smoking comparing smokers with nonsmokers.

CIRCULATORY RESPONSE OF SUBJECTS GROUPED BY PARENTAL HISTORY

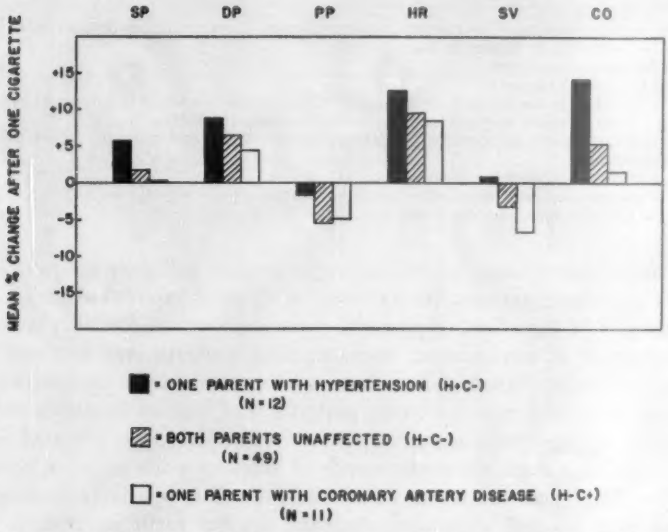

FIG. 5. The patterns of circulatory response to smoking among subjects with parental history of hypertension, subjects with normal parents and subjects with parental history of coronary artery disease.

both parents unaffected by either hypertension or coronary artery disease was intermediate and closely resembled the mean circulatory response to smoking of the entire group. (Compare figure 5 with figure 1.) Subjects with both hypertension and coronary artery disease in their parental heritage did not show a distinctive pattern such as was observed when either parental disorder was present alone (table 3).

C. *Statistical Analysis:* For the statistical evaluation of these findings, some of which involve small numbers of subjects, it was deemed important to compare groups that were as homogeneous as possible in regard to the factors under consideration. Table 4 shows the distribution of subjects by sex, by smoking habits and by parental history. It may be seen that

TABLE 4

Distribution of Subjects by Sex and Smoking Habits and by Parental History

Parental[1] History	Subjects								Total
	Males				Females				
	Smokers		Nonsmokers		Smokers		Nonsmokers		
	N		N		N		N		
H+ C+	5	#	3	⊥	1	⊥	0	⊥	9
H+ C−	9[2]	#	2	⊥	1	⊥	0	⊥	12
H− C+	10	#	1	⊥	0	⊥	0	⊥	11
H− C−	28[3]	# x o	14	o	7	x	0	⊥	49
Total	52		20		9		0		81[4]

[1] H = hypertension, C = coronary artery disease, + = definitely present in at least one parent, − = definitely absent in both parents.

[2] 8 for second cigarette.

[3] 26 for second cigarette.

[4] In 30 subjects the history for H and/or C was questionable or unknown in one or both parents. Two subjects were excluded because of parental diabetes.

= groups analyzed for effect of parental hypertension and coronary artery disease and their interaction.

x = groups analyzed for effect of sex.

o = groups analyzed for effect of smoking habits.

⊥ = groups excluded from analysis.

the *male smokers* comprise the only group with sufficient subjects of each type of heritage to support the statistical analysis of parental history. Hence, the analysis of the effect of parental hypertension and coronary artery disease, alone or in combination, upon smoking patterns was confined to this group. Since no female nonsmokers were present in the sample, the effect of being a smoker upon smoking patterns was studied in males only, and then only in those with negative parents. Similarly, the effect of sex was studied only through the performance of smokers with negative parents.

The differences in mean values between the relatively homogeneous groups thus selected were computed and are set forth in table 5. Com-

TABLE 5

The Effect of Each of the Five Attributes upon Each of the 21 Measurements

Level	Attribute	Systolic Pressure		Diastolic Pressure		Pulse Pressure		Heart Rate		Stroke Volume		Cardiac Output		Cardiac Index	
		mm. Hg	t	mm. Hg	t	mm. Hg	t	beats /min.	t	c.c.	t	c.c./min.	t	C.O. /S.A.	t
Control	Sex	+2.5	0.51	−4.2	1.36	+6.8	1.63	−9.0	1.88	+20.2	*3.25*	+513.7	1.03	−0.25	0.94
	Smoking	−8.5	*2.49*	−2.2	0.97	−6.2	1.93	+4.8	1.28	+0.7	0.14	+498.7	1.29	+0.28	1.39
	Parental hypertension	+6.4	1.84	+4.1	1.72	+2.3	0.70	+2.2	0.59	+13.6	*2.77*	+1,357.0	*3.43*	+0.48	*2.31*
	Parental coronary artery disease	+6.4	1.84	+2.3	0.95	+4.1	1.26	+3.8	1.04	− 7.1	1.45	−171.7	0.43	−0.12	0.57
	Parental hypertension and coronary artery disease	+3.2	0.91	−1.1	0.93	+4.3	1.34	−1.2	0.33	+ 8.0	1.63	+505.9	1.28	+0.21	1.00
First cigarette	Sex	−8.0	*3.21*	−0.9	0.41	−7.0	*2.41*	−5.3	1.59	+ 5.0	1.63	+149.0	0.58	+0.05	0.37
	Smoking	−1.1	0.58	+0.4	0.24	−1.5	0.68	0.0	0.00	+ 3.3	1.42	+190.9	0.96	+0.10	0.97
	Parental hypertension	+3.3	1.70	+2.0	1.09	+1.4	0.59	+4.2	1.59	0.0	0.01	+469.7	*2.31*	+0.23	*2.18*
	Parental coronary artery disease	−2.8	1.40	−1.3	0.70	−1.5	0.64	−0.8	0.29	− 6.9	*2.87*	−587.5	*2.89*	−0.30	*2.93*
	Parental hypertension and coronary artery disease	−2.9	1.50	0.0	0.01	−3.0	1.28	+0.8	0.32	− 2.4	1.01	−175.1	0.86	−0.08	0.79
Second cigarette	Sex	+1.5	0.44	−3.3	1.90	+4.8	*2.03*	−1.6	0.72	− 2.6	0.61	−190.9	0.59	−0.10	0.64
	Smoking	−1.2	0.56	−1.1	0.63	0.0	0.00	+2.9	1.54	− 4.9	1.52	− 11.8	0.05	+0.01	0.05
	Parental hypertension	−0.8	0.55	−1.5	1.06	+0.7	0.38	−2.4	1.27	− 2.5	0.78	−439.5	1.70	−0.24	1.96
	Parental coronary artery disease	+2.3	1.54	+3.3	*3.09*	−1.0	0.58	−1.3	0.72	+ 3.9	1.17	+ 42.1	0.16	+0.02	0.16
	Parental hypertension and coronary artery disease	+1.4	0.96	+1.3	0.92	+0.1	0.08	−2.4	1.27	− 2.0	0.61	−285.1	1.10	−0.14	1.14

parisons for the five attributes have been uniformly carried out in the following order:

1. Sex: males versus females
2. Smoking: smokers versus nonsmokers
3. Parental hypertension: H + C — subjects versus H — C — subjects *
4. Parental coronary artery disease: H — C + subjects versus H — C — subjects
5. Parental hypertension and coronary artery disease: H + C + subjects versus H — C — subjects

Thus table 5 shows that at the control level, the mean heart rate of the male subjects was nine beats per minute slower than that of the female subjects, and that after the first cigarette the cardiac output of subjects with hypertensive parental history rose 469.7 c.c. more than did that of subjects with negative parents.

Table 5 also shows the t values for the observed differences in each comparison. Those values which exceed 2.00 are given in italics. During the control period the stroke volume, cardiac output and cardiac index of subjects with parental hypertension were substantially larger than those of subjects with negative parental history. The outstanding findings after smoking one cigarette may be stated as follows:

1. Systolic pressure rose more in women than in men.
2. Pulse pressure narrowed more in men than in women.
3. There were no significant differences to be found between smokers and nonsmokers.
4. Subjects with parental hypertension showed a greater increase in cardiac output and cardiac index than did subjects with negative parents.
5. Subjects with parental coronary artery disease showed a much smaller increase in cardiac output and cardiac index than did subjects with negative parents.

It would appear that the cardiac output, at the first cigarette level, achieves the best discrimination between subjects with hypertensive parental history and negative parental history, and also between subjects with coronary parental history and negative parental history.

Discussion

These results emphasize the fact that there is no universal pattern of circulatory response to smoking. The over-all effect of tobacco appears to be a somewhat individual matter, and surprising variations are found even in such a relatively homogeneous group as healthy medical students.

* The parental history of the subjects is designated by H, C, + and —, as in the footnote to table 4.

Conspicuous differences, in both the direction and the degree of change after smoking one cigarette, were found in all the variables studied. Where one variable changed notably in a given direction, the others tended to alter in characteristic fashion, thus attesting to the physiologic interrelationship of the seven circulatory determinants. While the occurrence of different reactions to smoking has been described by earlier investigators, attention has usually been focused upon a single circulatory determinant. People who were "hyperreactors" to smoking in one way or another have been said to have an "idiosyncrasy" to tobacco, but the meaning of this term is poorly understood, and little or nothing is known of the ultimate fate of such individuals.[24-29]

The present study has attempted to decipher the meaning of some of the unusual effects of smoking. The most challenging results arising out of it were found in the patterns associated with specific types of family history. Subjects with parental hypertension (H + C —), whose control cardiac output and cardiac index were large to begin with, showed more than twice as much increase in mean cardiac output after smoking one cigarette as did subjects with negative parental history, or, indeed, any other group analyzed in table 3. These H + C — subjects were unique in that the mean stroke volume did not decrease, as it did in all other groups, despite the acceleration of the heart. When it is noted that the mean diastolic pressure increase was also the highest of any group in table 3, and that the mean increase in systolic pressure and heart rate were only equaled or exceeded by the mean changes among the women, it seems fair to say that the offspring of hypertensive parents as a group showed hyperreactivity to smoking, which appeared to be both cardiac and vascular in origin. Actually, of the 12 H + C — subjects, all but one of whom were men, five, including Subject 56M67 in figure 2, showed general hyperreactivity; two subjects showed less general effects, yet had the characteristic increase in stroke volume and cardiac output, while the remaining five showed little or no tendency toward excessive changes after smoking. The fact that the H + C — subjects fell naturally into hyperreactive and nonreactive groups, rather than presenting graded characteristics, supports the possibility that genetic factors may play a rôle in these reaction patterns. Since each of these subjects had but one hypertensive parent, circulatory hyperreactivity would be expected to affect only a portion of the offspring, whatever the type of inheritance involved. That the offspring of hypertensive parents tend to have vasomotor hyperreactivity has been demonstrated by Hines, using a standardized cold pressor test.[30-33] Thomas has shown that, following exercise, subjects with parental hypertension may have both vasomotor and cardiac lability, and has found cardiac hyperreactivity in response to the cold stimulus as well as a pressor response.[12] No such relationship between familial hypertension and hyperreactivity to smoking has previously been described, but the studies indicating that there is a relationship between hyperreactivity to smoking and to

the cold pressor test, on the one hand, and those showing that hypertensive patients react more strongly to smoking than do normotensive subjects, on the other, are in harmony with the hypothesis that hyperreactivity appears more frequently in individuals who are the offspring of hypertensive parents and may be a precursor of hypertension in a given individual.[34]

Equally striking is the evidence that the 11 subjects with parental coronary artery disease (H — C +) (all were men and 10 were smokers) have distinctive patterns. As was seen in table 3, the control stroke volume, cardiac output and cardiac index of the H — C + group were low, whether compared with the subjects with negative history (H — C —), with the male group, or with smokers. Despite these initial low values, the stroke volume decreased markedly after one cigarette, and the cardiac output and cardiac index failed to increase half as much as they did in the other pertinent groups (table 3 and figure 5). Subject 54M78 in figure 2 was one of the H — C + group; in his case, the cardiac output actually decreased after smoking, as it did in several others. One can only speculate whether these characteristics contribute to the deterioration of form to be found among men with coronary artery disease in later life.[35-36] The reversibility of certain instances of abnormal form following the application of an abdominal binder suggests that there may be a critical threshold below which stroke volume cannot fall without losing the characteristic ballistic waves.[19, 36-38]

While the statistical evaluation of the family history data is difficult because of the small numbers of subjects in the groups with positive history, the mean differences given in table 5 dealing with groups which are homogeneous in regard to sex and smoking habits (females and nonsmokers having been excluded) corroborate the trends discussed above and illustrated in figure 5. In comparing the H + C — with the H — C — groups, and also the H — C + and H — C — groups, many of the t values are above 2.00 and several others approach 2.00 closely enough to warrant further observation in larger groups.

In regard to the comparison of smokers with nonsmokers, the blood pressure findings after the smoking of one cigarette do not seem to be different in the two groups, whether they are studied according to the percentage change after one cigarette (figure 4) or by absolute values (tables 3 and 5). This similarity may seem surprising in view of the fact that the regular smokers inhaled, whereas the nonsmokers "tried to inhale." However, it was shown by Lampson that, whether the subject inhaled or not, smoking a cigarette induced similar degrees of peripheral vasoconstriction in the first few minutes, but that after inhalation the effect lasted much longer.[7] Since all our observations were made immediately after smoking, any late variations in effect would not appear in this study. Differences in behavior of heart rate and cardiac output after smoking were found where all smokers and nonsmokers were compared (figure 4 and table 3).

but were not observed when contrasting only male smokers and nonsmokers with negative parental histories (table 5).

The findings of Levy and his associates in regard to the effect of intravenous nicotine are parallel to the present observations in certain important respects.[39] Studying normal persons of various ages and patients with coronary artery disease, they detected no significant differences between smokers and nonsmokers in the responses of heart rate, blood pressure or cardiac output. While comparison of coronary patients and normal subjects yielded no statistically valid differences in the degree of change in cardiac output after smoking, the *average* change of the seven coronary patients tested was definitely smaller than that of the eight normal persons, and the ranges of these two small groups showed relatively little overlap. These data from a somewhat different experiment fit well with the hypothesis that precoronary individuals and coronary patients show a *subnormal* increase in cardiac output after smoking or nicotine administration.

Summary

1. The effects of smoking upon the systolic pressure, diastolic pressure, pulse pressure, heart rate, stroke volume (as determined by the ballistocardiograph), cardiac output and cardiac index have been measured in 113 healthy medical students.

2. Statistically significant changes occurred in all measurements following the smoking of one cigarette.

3. The direction and degree of change after smoking varied greatly from subject to subject, so that striking individual differences in circulatory patterns were found.

4. Groups of individuals selected on the basis of similar changes in a single circulatory determinant had characteristic over-all patterns of change after smoking differing from those of other groups.

5. The circulatory patterns of certain subgroups were compared. Among the more striking differences found were those associated with family history. Subjects with parental hypertension, whose control cardiac output and cardiac index were large to begin with, showed more than twice as great an increase in cardiac output and cardiac index as did subjects with negative parents. Likewise, subjects with a parental history of coronary artery disease showed very little increase in cardiac output and cardiac index, in contrast to subjects with negative parents. The significance of these findings is discussed.

Summario in Interlingua

Como parte de un studio del possibile precursores de hypertension e morbo de arteria coronari, le effecto del fumar de cigarrettas super le equilibrio circulatori esseva determinate in 113 studentes medical in bon stato de sanitate. Esseva mesurate

pression systolic, pression diastolic, pression de pulso, frequentia cardiac, volumine per pulso, rendimento cardiac, e indice cardiac, tanto durante un periodo de controlo como etiam immediatemente post le fumar de un prime e de novo de un secunde cigarretta. Un ballistocardiographo del typo Starr esseva usate pro le calculation del volumine per pulso secundo le methodo de Tanner.

Alterationes median de signification statistic occurreva in omne mesurationes post le fumar del prime cigarretta. Pauc alterationes additional esseva notate post le secunde cigarretta. Le direction e le grado del alterationes variava grandemente ab un individuo al altere, con le resultato que frappante differentias individual esseva trovate in le configurationes circulatori. Le gruppamento de individuos con simile alterationes de un specific determinante circulatori resultava in gruppos characterisate per distinctive aspectos del alterationes in general. Nos executava un comparation del aspectos de certe sub-divisiones de nostre gruppos. Le plus frappante differentias notate includeva differentias associate con le historia familial. Individuos con patre o matre hypertensive e characterisate per alte valores de controlo in rendimento cardiac e indice cardiac, monstrava, post fumar, plus que duple le rendimento cardiac e indice cardiac que esseva trovate in individuos con patre e matre sin hypertension. Del altere latere, individuos con un historia parental de morbo de arteria coronari monstrava, in contrasto con individuos con parentes negative, solmente minissime augmentos del rendimento cardiac e del indice cardiac.

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THE EFFECTS OF CHRONIC PENTAPYRROLIDINIUM-INDUCED HYPOTENSION ON RENAL HEMODYNAMICS AND ON THE EXCRETION OF WATER AND ELECTROLYTES IN HYPERTENSION *

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THE aggressive treatment of hypertensive disease has come to occupy a more prominent part in the clinician's interest. This is due to the availability of potent antihypertensive agents. In some instances the enthusiasm of the clinician has been dampened by the observation of increased renal insufficiency accompanying a marked reduction of blood pressure. The occurrence of uremia has been observed more commonly in patients treated with ganglionic blocking agents because: (1) the drugs are quite potent in reducing blood pressure, and (2) the patients requiring treatment with these agents are more likely to have severe hypertensive disease, which is accompanied by the higher incidence of renal insufficiency. The present study was designed to evaluate the effects of prolonged reduction of blood pressure in hypertensive patients with and without renal damage, during the therapeutic oral administration of pentapyrrolidinium bitartrate,‡ an agent which appears to have a more marked inhibitory action in the autonomic ganglia than does hexamethonium. The effect of hexamethonium in treatment of hypertension and its effect on renal hemodynamics and on water and electrolyte excretion have been studied previously,[1] and a significant reduction in blood pressure was observed which was not accompanied by a reduction in renal flow except in one patient with severe hypertension and marked renal damage.

METHOD

Eleven patients with hypertension were studied by measurements of glomerular filtration rate (inulin clearance), renal plasma flow (para-aminohippurate clearance), and maximal tubular excretory capacity (TmPAH). The rates of urine formation, sodium excretion, potassium excretion and changes in blood pressure were observed. The technics of renal function studies and the methods of analysis have been described previously.[2] The control determinations of glomerular filtration rate (GFR), renal plasma flow (RPF), and tubular excretory capacity (TmPAH) consisted of three

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10 minute periods in the recumbent position. The patients were then given pentapyrrolidinium orally four times daily to establish a significant reduction of mean blood pressure in the recumbent position (mean blood pressure = diastolic blood pressure plus one third of pulse pressure). After an interval of at least one month the "drug" studies were repeated in precisely the same fashion as the control studies. Blood pressures were determined with a sphygmomanometer. The patients were admitted to the hospital several days prior to both groups of function studies and placed on an 800 mg. sodium diet. Between studies they were instructed in the 800 mg. sodium diet and followed on an out-patient basis.

TABLE 1

Effect of Oral Pentapyrrolidinium on Blood Pressure and Renal Function

Patient	Dx*	Age	Mean Blood Pressure† mm. Hg		Glomerular Filtration Rate ml./min.		Renal Plasma Flow ml./min.		Tubular Excretory Capacity mg./min.	
			C	D	C	D	C	D	C	D
J. F.	Chr. Gl.	42	143	98	61	74	298	617	90	103
J. B.	HVD	47	133	110	143	121	677	664	126	124
A. G.	HVD	46	160	120	83	99	531	689	110	131
A. B.	HVD	50	148	125	71	66	678	702	96	79
R. B.	HVD	41	145	108	93	105	697	729	90	89
D. T.	HCVD	42	128	114	75	69	457	583	73	73
M. J.	HCVD	63	163	148	72	59	349	317	74	95
L. A.	HCVD	49	158	137	69	69	400	400	108	85
W. McW.	HVD	43	130	103	82	69	465	381	120	155
T. E.	HCVD	56	160	118	90	78	445	403	72	98
G. C.	HCVD	42	140	123	72	67	407	595	81	80
Mean			146	118	83	80	491	553	95	101
Mean % of control				81		96		113		106
P Value				<.001		>.1		>.1		>.1

* HVD, Hypertensive vascular disease; HCVD, Hypertensive cardiovascular disease; Chr. Gl., Chronic glomerulonephritis.

† Mean blood pressure = Diastolic pressure plus ⅓ of the pulse pressure; C—Control recumbent; D—Drug recumbent.

RESULTS

A. *Effect of Oral Pentapyrrolidinium on Blood Pressure and Renal Function:* The data are presented in tabular form, and mean values have been calculated for the control state and the state after drug administration. The data have been statistically analyzed by the application of Student's "t" test and its resultant "p" value has been recorded.

As shown in table 1, pentapyrrolidinium produced an average reduction of mean blood pressure (MBP) to 81% of the control (146 to 118 mm. Hg) observations. This was highly significant ($p = <.001$). This was not associated with a significant change in glomerular filtration rate (GFR) (96% of control), maximal tubular excretory capacity for PAH (TmPAH) (106% of control), or in renal plasma flow (RPF) (113% of control).

TABLE 2

Effect of Oral Pentapyrrolidinium on Hematocrit, Renal Blood Flow and Renal Vascular Resistance

Patient	Hematocrit*		Renal Blood Flow ml./min. = $\frac{RPF}{1 - Hct}$		Renal Vascular Resistance × 10²†	
	C	D	C	D	C	D
J. F.	40	37	495	978	289	100
J. B.	45	44	1,232	1,186	108	92
A. G.	41	42	899	1,188	178	101
A. B.	41	43	1,172	1,232	126	101
R. B.	43	46	1,218	1,350	119	80
D. T.	44	43	816	1,024	156	111
J. M.	41	41	623	537	262	276
L. A.	45	45	727	728	217	188
W. McW.	44	44	838	680	155	151
T. E.	45	42	809	702	198	168
C. G.	40	40	702	993	199	124
Mean	43	43	866	963	182	136
Mean % of control		100		111		75
P Value		>.1		>.1		<.05

* See table 1 for definition of symbols.
† Renal vascular resistance = Mean blood pressure/renal blood flow.

The constancy of renal blood flow (RPF/1 minus hematocrit) (RBF) associated with a reduction in mean blood pressure yields an average decrease in renal vascular resistance of 25% ($p = <.05$) (RVR = MBP/RBF) (table 2). The hematocrit showed no significant change.

TABLE 3

Effect of Oral Pentapyrrolidinium on Water and Electrolyte Excretion and on Plasma Creatinine and Creatinine Excretion

Patient	Urine Volume ml./min.		Na Excretion mEq./min.		K Excretion mEq./min.		Plasma Concentration mEq./L. Na		Plasma Concentration mEq./L. K		Ccr		Plasma Creatinine	
	C	D	C	D	C	D	C	D	C	D	C	D	C	D
J. F.	4.6	5.9	163	50	73	58	121	127	4.3	2.9	68	82	1.4	1.2
J. B.	7.0	14.0	209		96		133		5.9		146	112	1.0	1.3
A. G.	10.1	10.7		109		92					87	113	1.4	0.9
A. B.	10.0	2.0		77		43		129			74	73	1.2	1.1
R. B.	15.0	5.6	257	49	64	123	162	133	4.6	5.2	106	117	1.2	1.1
D. T.	14.0	8.0	69	68	40	10	135		5.0		75	76	1.6	1.6
J. M.	7.8	5.0	74	78	75	54	136	134	5.0	4.3	85	66	0.9	1.3
L. A.	4.5	8.7		69		52		128		4.5	80	77	1.2	1.2
W. McW.	8.4	11.5	163		56		128		4.7		91	81	1.4	1.5
T. E.	15.0	12.0	200	115	55	93		159		5.3	92	92	1.4	1.4
G. C.	8.4	7.1	238	109	57	67	147	117	6.1	5.4	76	75	1.2	1.4
Mean	9.5	8.2	172	80	65	66	137	132	5.1	4.6	89	88	1.26	1.27
Mean % of control		86		47		101		96		90		99		101
P Value		>.1		<.05		>.1		>.1		>.1		>.1		>.1

Na = Sodium
K = Potassium.

B. *Effect of Oral Pentapyrrolidinium on Water and Electrolyte Excretion:* Following a period of therapy with pentapyrrolidinium, urine volume was reduced from an average of 9.5 ml./min. to 8.2 ml./min. (86% of control) (table 3). Sodium excretion decreased markedly, from 172 mEq./min. to 80 mEq./min. (47% of control). Potassium excretion was not significantly altered. Plasma sodium concentration decreased slightly, from 137 mEq./L. to 132 mEq./L. (96% of control) and plasma potassium concentration decreased from 5.1 to 4.6 mEq./L. (90% of control). These electrolyte changes were not statistically significant (see discussion). Creatinine clearances and plasma creatinine concentrations were not significantly altered.

C. *Effect of Oral Pentapyrrolidinium in a Patient with Severe Renal Damage:* Included in the present study was a 40 year old Negro male with

TABLE 4

Effect of Oral Pentapyrrolidinium on Renal Function, Renal Vascular Resistance and Water and Electrolyte Excretion in a Single Patient with Malignant Hypertensive Cardiovascular Disease

(F. M., 47 year old Negro male)	Control	Drug	% of Control
Mean blood pressure	154	140	90.9
Glomerular filtration rate	21	18	85.7
Renal plasma flow	92	54	58.7
Filtration fraction ($\times 10^2$)	23	33	143.5
Renal blood flow	158	83	52.5
Renal vascular resistance ($\times 10^3$)	975	1687	173.0
Tubular excretory capacity	22	21	95.4
GFR/TmPAH ratio	1.07	.86	80.4
Hematocrit	35	35	100
Urine volume	4.5	2.6	57.8
Sodium excretion	205	139	67.8
Potassium excretion	50	46	92.0
Plasma sodium	131	133	101.5
Plasma potassium	6.2	5.3	85.5
Creatinine excretion	25	26	104.0
Plasma creatinine	5.3	4.3	81.1

malignant hypertensive cardiovascular disease. Changes occurring in renal hemodynamics and water and electrolyte excretion in this patient before and after therapy with oral pentapyrrolidinium are listed in table 4. Renal damage already existed in this patient, as indicated by the elevated plasma creatinine. Renal plasma flow decreased to 59% of control, with a decrease of renal blood flow to 52% of control. Concomitantly, renal vascular resistance increased to 173% of control. These changes contrast sharply with those seen in the 11 patients with less severe hypertensive disease, described above.

DISCUSSION

Previous work has shown that oral hexamethonium is capable of producing a significant reduction in blood pressure without decreasing glo-

merular filtration rate, renal plasma flow or TmPAH in the supine position. The present data indicate that such is also the case during prolonged oral pentapyrrolidinium therapy. There is also a significant reduction of renal vascular resistance. Moderate preëxistent renal damage did not appear to alter this response. However, in one patient with severe hypertension and marked renal damage, a fall in blood pressure was accompanied by a marked decrease in renal plasma flow and a marked increase in renal vascular resistance. This would seem to indicate that reduction of renal vasoconstriction may occur when treatment with pentapyrrolidinium is used in all hypertensive patients except those with severe renal damage.

This information is of clinical value. It is generally agreed that the majority of patients with moderate or severe hypertensive disease manifested by a consistent elevation of the diastolic blood pressure greater than 120 mm. of mercury will suffer complications involving the two large target organs, the heart and the brain. There will be a smaller group of patients who will suffer complications of their hypertension involving the other common target organ, the kidney. It is our opinion that this group of patients with moderate or severe hypertensive disease should receive the benefit of potent antihypertensive therapy, and that the most effective agents at the present time are the ganglionic blocking agents such as pentapyrrolidinium, hexamethonium and, most recently, mecamylamine. However, when the patient being treated with these drugs presents evidence of moderate or severe renal damage, as determined by such clinical tests as the 15-minute phenolsulfonphthalein (PSP) excretion test, concentration tests or blood urea nitrogen (BUN) and creatinine levels, he should be closely observed. We believe that renal function is most simply followed by serial blood urea nitrogen (BUN) determinations when the blood pressure is being reduced by these potent therapeutic agents.

A moderate decrease of water excretion and a marked decrease of sodium excretion were noted. A slight decrease in plasma sodium concentration was also noted. Although other factors may exist, decreased sodium intake due to failure of the patient to consume his entire diet while receiving pentapyrrolidinium appears to be the most probable reason for the decrease in sodium excretion. In any event, this observation was accompanied by no significant clinical change.

Summary and Conclusions

Eleven patients with hypertension were observed during oral pentapyrrolidinium therapy.

In the supine position there was a reduction in blood pressure after pentapyrrolidinium without a reduction in renal plasma flow, glomerular filtration rate or tubular excretory capacity. These observations indicate that the renal blood vessels in patients with hypertension are still able to respond to general hemodynamic factors which result in vasodilatation.

Pentapyrrolidinium when used orally in the prolonged treatment of hypertension appears to be of considerable value. It did not appear to produce significant alteration of clinical status in terms of impaired excretion of nitrogenous substances or in the retention of sodium and water in patients showing no evidence of renal disease prior to therapy.

Summario in Interlingua

Dece-un patientes con hypertension esseva investigate per medio de discrete studios de function renal in le stato de controlo e de novo post un significative reduction del pression median de sanguine, effectuate per un curso de al minus un mense de pentapyrrolidinium in administrationes oral.

Le studios de function renal esseva executate con le patientes in decubito dorsal. In le patientes con leve o moderate grados de pre-existente damno renal, nos constatava un significative reduction del pression sanguinee sin significative grados de reduction del fluxo de plasma renal e del capacitate tubulo-excretori o de relentation del filtration glomerular. Iste observationes pare indicar que le renal vasos sanguinee in patientes con hypertension es ancora capace a responder al effecto de factores hemodynamic general que resulta in vasodilatation.

In contrasto con le supra-mentionate constatationes, il esseva trovate in un patiente con maligne morbo cardiovascular hypertensive e marcate grados de damno renal que il habeva un marcate reduction del fluxo de plasma renal e del fluxo de sanguine renal, accompaniate per un marcate augmento del resistentia reno-vascular.

Ergo, pentapyrrolidinium in administrationes oral pareva esser de considerabile valor in le tractamento a longe durantia de hypertension. Illo non pareva producer alterationes significative del stato clinic quanto al excretion de substantias nitrogene o al clearance de natrium e aqua in patientes exhibiente nulle signo de morbo renal ante le institution del therapia.

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THE CLINICAL SIGNIFICANCE OF HYPERGLOBULINEMIA. I. DIAGNOSTIC IMPLICATIONS *

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IN certain diseases the occurrence of hyperglobulinemia has been noted so frequently that the laboratory finding of an elevated serum globulin, without evident clinical explanation, will usually provoke an intensive diagnostic search for evidence of their presence. Among the conditions regularly associated with hyperglobulinemia are multiple myeloma, sarcoidosis, collagen disease, cirrhosis of the liver, kala-azar, lymphogranuloma venereum and certain other infections. The first three of these diseases in particular may often be unsuspected following routine clinical examinations, and are found only after the discovery of hyperglobulinemia gives the first clue leading to the diagnosis.

At many hospitals the quantitative measurement of serum total protein, with its separation into albumin and globulin portions, has become a frequent laboratory determination. In the Grace-New Haven Community Hospital the test is most commonly done to provide the serum total protein and albumin levels for evaluating patients with malnutrition, dehydration, edema or ascites. Albumin values are sometimes helpful in interpreting serum calcium and serum protein-bound iodine results, while the albumin-globulin relationship is frequently used as a liver function test.

Although the total protein-albumin-globulin determination is seldom done merely to provide globulin values for diagnostic purposes, the finding of an elevated serum globulin may, as noted, lead to further diagnostic consideration. In the course of observations in a general hospital where the TP with A/G measurement is frequently made, we noted many patients who had an elevated serum globulin value and were therefore suspected of having one of the diseases mentioned above. They were accordingly subjected to a number of diagnostic procedures, among them roentgenograms of the chest and bones, liver function tests, L. E. cell preparations, Frei tests, and bone marrow aspiration. In difficult problems, lymph node, muscle or liver biopsies were sometimes performed.

In some of these patients the studies confirmed the diagnostic suspicions. In many others, however, the results were essentially negative and nonproductive. In this latter group of patients the incidental chemical abnormality had thus led to a barrage of tests which shed no new light on the

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diagnosis and left the original clinical impression unchanged. The frequency with which these studies were nonproductive raised the question of whether any real *diagnostic* significance could be attached to the isolated finding of an increased serum globulin in the absence of clinical explanation.

It seemed desirable, therefore, to determine (1) how often hyperglobulinemia occurs without being due to some "specific" disease; (2) whether there is some globulin value at which the finding becomes diagnostically significant, and (3) how vigorously clinicians should carry out their diagnostic pursuits of the etiology of this incidental laboratory finding.

Material and Methods

In the medical chemistry laboratory of this hospital the total protein determination and albumin-globulin fractionation are done upon serum drawn under oil from patients in the postabsorptive state. The total protein determination is done by the biuret method of Gornall et al.,[1] with regular daily spot checks using Kjeldahl's technic. Lipemic or jaundiced sera give falsely high results in biuret determinations of total protein and are always measured by Kjeldahl's methods. The globulin is salted out by the method of Cohn and Wolfson,[2] and a biuret measurement is made upon the albumin in the filtrate. The normal range of values is as follows:

Total protein:	6.3–7.7 gm. per 100 ml.
Albumin:	3.7–4.8 gm. per 100 ml.
Globulin:	2.0–3.9 gm. per 100 ml.

It should be noted that the upper limit of normal for serum globulin in our laboratory is 3.9 gm.%, which is slightly higher than the usual value (3.0 gm.%) found in the older literature. This is because the older technics of A/G fractionations, which are still in vogue in many present-day laboratories, use some variant of the Howe [3] method. The latter has been shown by electrophoretic analyses [4, 5, 6] to separate some alpha globulin along with the albumin fraction, producing artificially low results for total serum globulin. Consequently, newer technics, which involve only changes in the nature and concentration of the salting-out agent, have been adopted by many laboratories and have been in use here since 1948. These new methods have shown excellent agreement with simultaneous electrophoretic analyses.

Using 3.9 gm.% as the upper limit of normal for serum globulin, we searched the laboratory files for the names of all individuals who, during the calendar year 1953, were found at any time to have a serum globulin of 3.9 or higher. This yielded 394 names, and the charts of these patients were studied carefully. All had been admitted to the private or ward services, or had been seen in the clinics of the Grace-New Haven Community Hospital. In addition to biographic data, the charts were abstracted for

pertinent laboratory determinations, including hemoglobin measurement, urinalysis, liver function tests, serologic tests and many others,* as well as the total protein with A/G values. Each patient was carefully considered for such clinical features as hepatosplenomegaly, lymphadenopathy, fever, edema, malnutrition, dehydration and therapeutic measures. Finally, the ultimate diagnosis or diagnoses were noted, using histologic evidence whenever available.

Each case was then analyzed and given a *single* diagnostic title. When patients had several diseases, those known to produce hyperglobulinemia were designated as primary. If more than one "hyperglobulinemic" disease was present (e.g., pneumonia and syphilis), the one responsible for hospitalization was chosen. Table 1 lists the classification of diseases known specifically to be associated with hyperglobulinemia. The diagnostic criteria for some of these diseases are self-evident; others require further explanation. In the presence of gall-bladder or pancreatic disease, the diagnosis of "other liver disease" was made only when significant hepatic involvement appeared to be present. The diagnosis of "nonmetastatic cancer" was made only if there was no evidence of extension beyond local or regional sites. "Lymphomas" included leukemia as well as the lymphatic neoplasms. Hepatomas or other primary liver carcinomas were classified as "metastatic carcinoma," † to simplify the later analysis of liver function tests. In the infectious disease group, "syphilis" required unequivocal evidence of the disease with inadequate past treatment and no other condition which might claim priority for the etiology of the high globulin, and "tuberculosis" required evidence of active disease. Far-advanced but inactive tuberculosis was considered to be "chronic pulmonary disease."

A striking number and variety of cases, however, could not be fitted into the above categories and were listed as "unclassified." In this group, when two or more diseases were present the primary diagnosis was assigned to the prevailing clinical situation which appeared to be responsible for the patient's admission to the hospital.

For each case, regardless of its diagnostic classification, the various available albumin-globulin determinations were then reviewed and a single set of values was chosen to be representative. The selections were made in the following way: If only one of the recorded globulin determinations was 3.9 gm.% or higher, that value was chosen. If several abnormally high globulin values had been noted, the one selected was generally that which was closest to the date of an admission to the hospital. In certain cases,

* Although serum globulin fractionation by paper electrophoresis was performed for some of the patients, the data available are insufficient to warrant detailed analysis and will not be further considered here.

† An arbitrary decision was necessary here. We chose to assume that any disseminated carcinoma might well have hepatic metastases, whether or not these were clinically evident. The "metastatic cancer" category is thus made to include all hepatic neoplasia, primary or secondary.

a slightly later set of A/G values was taken in order to correspond to liver function tests drawn on the same date. In a few rare cases, where the 1953 globulin value was only slightly raised but where a previous year's determination was markedly elevated (e.g., rheumatic fever in remission), one of the very high values was chosen. In one or two instances (e.g., multiple myeloma), where the globulin may have been only slightly increased for a long period of time and then have jumped to marked elevation, the first of the extremely high values was selected.

Each case was thus labeled with a single diagnosis and a single representative albumin-globulin determination.

TABLE 1

Specific "Hyperglobulinemic" Diseases

This table lists diseases which have frequently been reported in conjunction with hyperglobulinemia, cites some of the reporting sources, and indicates the categories in which they have been classified in this paper.

Laennec's cirrhosis[7, 8]
Other liver disease[7, 8]
Non-metastatic carcinoma[9–14]
Metastatic carcinoma[9–14]
Multiple myeloma[15, 16]
Lymphomas[13, 17–19]
Collagen disease
- Acute rheumatic fever[20]
- Acute glomerulonephritis[21]
- Systemic lupus erythematosus[22–24]
- Rheumatoid arthritis[25–28]
- Periarteritis nodosa[29]
- Scleroderma[30]

Sarcoidosis[11, 31–34]
Chronic pulmonary disease[35]
Infectious diseases[36]
- Kala-azar[37, 38]
- Lymphogranuloma venereum[39–42]
- Filariasis[43]
- Leprosy[44]
- Pneumonia[45–48]
- Schistosomiasis[49]
- Subacute bacterial endocarditis[50]
- Syphilis[46, 51, 52]
- Trichinosis[53, 54]
- Tuberculosis[11, 55, 56]

RESULTS

Table 2 shows the diagnoses and albumin-globulin data of those patients with specific "hyperglobulinemic" diseases. They are listed, within the described categories, in order of ascending globulin values. A more detailed consideration of this table shows the following points of interest:

1. In the group designated "other liver disease," the higher globulin values are more prevalent in cases with primary parenchymatous disease than in those secondary to extrahepatic pathology. Extremely high globulin values in biliary cirrhosis, as noted here, have been described [9] in the past.

TABLE 2

Diagnoses and Serum Protein Data in Patients with Specific "Hyperglobulinemic" Diseases

Age Race Sex	Diagnosis	Method of Diagnosis	TP	A	G
	Laennec's Cirrhosis				
74 W M	Laennec's cirrhosis; ascites	C	5.50	1.58	3.92
46 W M	Laennec's cirrhosis; anemia	C	7.05	3.09	3.96
46 W M	Laennec's cirrhosis; jaundiced	C	6.38	2.39	3.99
27 W F	Laennec's cirrhosis; jaundiced	C	7.45	3.44	4.01
59 W M	Laennec's cirrhosis; ASHD; Pulm. infarct	LB	6.07	2.01	4.07
52 W F	Laennec's cirrhosis; RUQ pain	LB	5.51	1.43	4.08
59 W M	Laennec's cirrhosis; ascites	LB	6.53	2.41	4.12
53 W M	Laennec's cirrhosis; comatose	A	5.82	1.65	4.17
48 W M	Laennec's cirrhosis; healing	LB	6.86	2.63	4.23
52 N F	Laennec's cirrhosis; toxic goiter	A	7.01	2.77	4.24
60 N F	Laennec's cirrhosis; diab. mellitus	LB	7.05	2.80	4.25
62 W M	Laennec's cirrhosis	C	7.16	2.91	4.25
56 W M	Laennec's cirrhosis; bleeding esoph. var.	A	6.06	1.77	4.29
56 W M	Laennec's cirrhosis; duodenal ulcer	LB	6.43	2.09	4.34
47 W M	Laennec's cirrhosis; ascites, esoph. var.	C	6.37	1.97	4.40
28 N F	Laennec's cirrhosis; jaundiced	LB	6.38	1.91	4.47
39 W M	Laennec's cirrhosis; comatose	C	5.83	1.34	4.49
66 W M	Laennec's cirrhosis; skin rash, ? etiol.	C	7.29	2.78	4.51
46 W M	Laennec's cirrhosis; comatose	LB	6.35	1.84	4.51
52 W F	Laennec's cirrhosis; esoph. varices	C	7.10	2.55	4.55
35 N F	Laennec's cirrhosis; acute pancreatitis	LB	7.00	2.41	4.59
62 W F	Laennec's cirrhosis; ASHD	LB	6.08	1.38	4.70
32 N M	Laennec's cirrhosis; diabetes mellitus	LB	6.77	2.04	4.73
59 W M	Laennec's cirrhosis; FUO	C	7.05	2.27	4.78
67 W M	Laennec's cirrhosis; ASHD	C	7.41	2.61	4.80
54 W F	Laennec's cirrhosis; nausea, vomiting	LB	7.87	3.06	4.81
68 W M	Laennec's cirrhosis; portal vein thromb.	A	6.61	1.80	4.81
40 N F	Laennec's cirrhosis; ascites	LB	6.04	1.13	4.91
74 W M	Laennec's cirrhosis; ascites, recurrent	LB	7.70	2.73	4.97
44 N M	Laennec's cirrhosis; HCVD	LB	7.96	2.96	5.00
63 W M	Laennec's cirrhosis; ascites	C	6.53	1.52	5.01
39 W F	Laennec's cirrhosis; jaundiced	LB	7.70	2.61	5.09
53 W M	Laennec's cirrhosis; ? hepatoma	C	7.05	1.93	5.12
55 W F	Laennec's cirrhosis; anorexic	LB	7.31	2.09	5.22
62 W M	Laennec's cirrhosis; ascites, esoph. var.	C	7.20	1.47	5.73
49 W F	Laennec's cirrhosis; improving on rest	LB	8.69	2.83	5.86
59 W F	Laennec's cirrhosis; comatose	A	7.34	1.40	5.94
	Other Liver Disease				
52 W F	Obstructive jaundice, ? etiology	C	6.96	3.06	3.90
41 W F	Gangrenous cholecystitis	SP	7.63	3.71	3.92
78 W F	Chr. cholecystitis and cholangitis	C	7.15	3.14	4.01
68 W F	Portal vein thrombosis; cholangitis	A	6.72	2.71	4.01
48 N M	Acute and chronic cholangitis	LB	7.40	3.30	4.10
43 W M	Early biliary cirrhosis	LB	6.75	2.61	4.14

Abbreviations used: W—White; N—Negro; M—Male; F—Female; ASHD—Arteriosclerotic Heart Disease; HCVD—Hypertensive Cardiovascular Disease; IRHD—Inactive Rheumatic Heart Disease; CVA—Cerebrovascular Accident; *—Diabetes Mellitus; A-S—Arteriosclerosis; FUO—Fever of Unknown Origin; GB—Gall-Bladder; CA—Carcinoma; Met.—Metastatic.

C—Clinical; A—Autopsy; B—Biopsy; LB—Liver Biopsy; SP—Surgical Pathology; BM—Bone Marrow; S—Surgery.

Note: The term "clinical" as used under "Methods of Diagnosis" includes bacteriologic, roentgenologic, chemical and other data, as well as routine examinations.

TABLE 2—*Continued*

Age Race Sex	Diagnosis	Method of Diagnosis	TP	A	G
	Other Liver Disease (*continued*)				
67 W F	Acute and chronic cholecystitis	SP	7.30	3.09	4.21
55 W F	Posthepatitic cirrhosis	LB	6.50	2.22	4.28
40 N F	Chronic pancreatitis; fatty liver	A	6.72	2.41	4.32
61 W F	Chronic cholecystitis and cholelithiasis	SP	7.70	3.38	4.32
57 W F	Obs. jaundice 2° to bile duct strict.	C	7.30	2.80	4.50
50 W M	Chronic pancreatitis	S	7.50	2.93	4.57
89 W M	Chr. cholecystitis; rupture of GB	A	6.90	2.20	4.70
76 N F	Homologous serum hepatitis	C	7.17	2.46	4.71
25 W F	Postnecrotic cirrhosis	A	6.92	2.21	4.71
58 W M	Infectious hepatitis	LB	7.23	2.51	4.72
64 W F	?-Biliary cirrhosis	C	7.05	2.32	4.73
58 W M	Subacute hepatitis	C	6.52	1.55	4.97
54 W F	Biliary cirrhosis	LB	7.27	2.11	5.16
65 W F	Biliary cirrhosis	LB	7.20	1.95	5.25
54 W F	Postnecrotic cirrhosis	C	8.49	1.50	6.99
	Nonmetastatic Cancer				
61 W F	Fibrosarcoma of rib	B	6.90	2.98	3.92
54 W M	Mixed salivary gland tumor of tongue	B	7.00	3.06	3.94
53 W M	Epidermoid carcinoma of lung	A	7.35	3.41	3.94
49 N M	Epidermoid carcinoma of lung	SP	6.53	2.58	3.95
72 W M	Adenocarcinoma of rectum	SP	6.50	2.55	3.95
79 W F	Adenocarcinoma of colon	SP	7.25	3.30	3.95
58 W M	Pleural mesothelioma	B	7.05	3.09	3.96
65 W M	Adenocarcinoma of stomach	SP	6.82	2.83	3.99
68 W F	Adenocarcinoma of colon	SP	6.96	2.69	4.00
62 N F	Carcinoma of cervix	SP	6.53	2.51	4.02
54 N M	Epidermoid carcinoma of bladder	SP	7.25	3.21	4.04
61 W M	Adenocarcinoma of stomach	SP	6.53	2.48	4.05
66 W M	Epidermoid carcinoma of mouth	B	6.15	2.06	4.09
65 W M	Transitional cell CA of bladder	B	6.33	2.22	4.11
64 W M	Tumor of kidney (?-histology)	S	6.46	2.34	4.12
93 W F	Adenocarcinoma of stomach	A	5.54	1.37	4.17
52 W M	Oat cell carcinoma of lung	B	6.90	2.71	4.19
60 W M	Epidermoid carcinoma of tonsil	SP	7.10	2.90	4.20
77 W M	Epidermoid carcinoma of lung	A	5.90	1.69	4.21
67 W M	Epidermoid carcinoma of tongue	B	6.28	2.04	4.24
67 W M	Retroperitoneal sarcoma	SP	6.28	2.02	4.26
71 W M	Carcinoma of larynx	SP	7.35	3.06	4.29
74 W F	Carcinoma of stomach	C	6.28	1.99	4.29
69 W F	Adenocarcinoma of cecum	SP	6.12	1.77	4.35
46 W F	Epidermoid carcinoma of cervix	SP	7.30	2.90	4.40
78 W M	Epidermoid carcinoma of esophagus	SP	6.77	2.38	4.41
70 W M	Adenocarcinoma of prostate	SP	6.15	1.71	4.44
50 W M	Carcinoma of lung	C	6.64	2.11	4.53
49 W F	Adenocarcinoma of breast	SP	7.76	3.24	4.52
60 W F	Epidermoid carcinoma of hypopharynx	SP	7.92	3.38	4.54
55 W F	Adenocarcinoma of breast	B	7.50	2.96	4.54
	Metastatic Cancer				
76 W M	Adenocarcinoma of lung, met. to bone	B	6.68	2.78	3.90
63 W M	Hepatoma	LB	5.99	2.09	3.90
46 W F	Adeno CA of breast, met. to bone	SP	6.82	2.91	3.91
65 W M	Adenocarcinoma in liver, ?-primary	LB	7.15	3.24	3.91

TABLE 2—*Continued*

Age	Race	Sex	Diagnosis	Method of Diagnosis	TP	A	G
			Metastatic Cancer (*continued*)				
79	W	M	Adeno CA of prostate, met. to bone	SP	6.46	2.55	3.91
31	W	M	Adeno CA of lung, met. to spinal cord	SP	7.35	3.41	3.94
79	W	M	Adeno CA of rectum, met. to liver	A	7.45	3.47	3.98
67	W	F	Adeno CA of breast, diffuse metas.	B	6.58	2.59	3.99
72	W	F	CA of uterus, met. to peritoneum	SP	6.33	2.30	4.03
79	W	F	Carcinoma of breast, met. to bone	C	6.36	2.27	4.09
64	N	F	Carcinoma of lung, met. to liver	C	5.78	1.60	4.18
61	N	M	Adenocarcinoma in liver, ?-primary	B	7.99	3.57	4.22
55	W	M	Colloid adeno CA, ?-primary	B	5.90	1.67	4.23
64	W	M	Anaplastic CA of lung, met. to liver	B	8.04	3.80	4.24
66	W	M	Epidermoid CA of lung, met. to bone	B	6.90	2.65	4.25
71	N	F	Adeno CA of breast, met. to bone and lung	SP	6.58	2.29	4.29
67	W	F	Met. CA in liver, probably from pancreas	LB	6.64	2.34	4.30
66	N	F	Anaplastic CA of rectum, widespread	SP	7.30	2.96	4.34
69	W	F	Adeno CA of liver, met. to lung	A	5.55	1.21	4.34
74	W	M	Adeno CA of cecum, widespread	A	6.33	1.97	4.36
53	W	M	Adeno CA of colon, met. to liver	SP	5.96	1.60	4.36
17	N	M	Cholangioma	LB	8.18	3.72	4.46
62	W	F	Metas. adeno CA, primary unknown	B	7.28	2.78	4.50
66	N	M	Epidermoid CA of esoph., met. to liver	A	7.70	3.20	4.50
66	W	M	Anaplastic CA in skin, bone; ?-primary	B	6.12	1.60	4.52
65	W	M	Adeno CA of rectum, met. to liver	SP	6.86	2.51	4.53
66	W	M	Epidermoid CA of esoph., met. to liver	A	6.77	2.13	4.64
62	W	M	Bronchogenic CA of lung, met. to liver	A	8.14	3.47	4.67
74	W	M	Metas. adeno CA in bone, ?-primary	B	5.96	1.23	4.73
74	W	M	CA of gall-bladder, met. to liver	A	7.49	2.68	4.81
55	W	M	Adeno CA of lung, widespread	A	7.35	2.48	4.87
64	W	M	Anaplastic CA in liver, ? from rectum	LB	8.30	2.95	5.32
74	W	F	CA in peritoneum, primary ? in ovary	B	8.94	1.58	6.96
			Multiple Myeloma				
66	W	M	Multiple myeloma-?	BM	7.60	3.67	3.93
55	W	F	Multiple myeloma	BM	6.58	2.65	3.93
70	W	M	Multiple myeloma; HCVD	BM	7.05	2.83	4.22
66	W	F	Multiple myeloma; ASHD	BM	7.89	2.96	4.91
70	W	F	Multiple myeloma; pneumococ. meningitis	BM	8.25	1.55	6.70
67	W	M	Multiple myeloma	BM	8.30	1.54	6.76
54	W	M	Multiple myeloma	BM	9.16	2.34	6.82
41	W	F	Multiple myeloma	BM	9.62	1.73	7.89
71	W	M	Multiple myeloma	BM	10.48	1.67	8.81
68	W	M	Multiple myeloma	BM	10.50	1.42	9.08
64	W	M	Multiple myeloma	BM	10.48	1.27	9.21
67	W	M	Multiple myeloma	BM	12.83	1.50	11.33
			Lymphomas				
71	W	M	Reticulum cell sarcoma	B	6.64	2.73	3.91
22	N	M	Acute myeloid leukemia	BM	7.65	3.33	4.32
68	W	M	Lymphocytic leukemia	BM	7.50	3.09	4.41
75	W	M	Subacute lymphatic leukemia	BM	7.16	2.13	5.03
29	W	M	Hodgkin's disease	B	6.53	1.33	5.20
52	W	M	Reticuloendotheliosis-?	B	7.50	2.06	5.44
69	W	M	Lymphocytic lymphoma	A	9.28	1.69	7.59

TABLE 2—*Continued*

Age Race Sex	Diagnosis	Method of Diagnosis	TP	A	G
	Collagen Disease				
27 W F	Acute glomerular nephritis	C	2.70	3.30	3.90
57 W F	Rheumatoid arthritis; ?-Lupus eryth.	C	6.90	2.98	3.92
65 W F	Acute glomerular nephritis	C	6.07	2.15	3.92
34 W F	Rheumatoid arthritis	C	6.72	2.68	4.04
47 W F	Acute rheumatoid arthritis	C	6.50	2.41	4.09
59 N F	?-Periarteritis nodosa	C	7.16	3.05	4.11
28 W M	Acute rheumatic fever	C	7.20	3.09	4.11
43 W F	Systemic lupus erythematosus	A	6.46	3.32	4.14
48 W F	Periarteritis nodosa	B	6.96	2.80	4.16
42 W M	Acute and chronic glom. nephritis	C	6.64	2.41	4.23
24 W M	Acute rheumatic fever	C	6.62	2.37	4.25
56 W F	Rheumatoid arthritis	C	6.28	2.02	4.26
19 W M	Acute rheumatic fever	C	7.35	3.04	4.31
32 N M	Acute rheumatoid arthritis	C	6.68	2.32	4.36
43 W F	Nodular vasculitis	B	7.56	3.09	4.47
65 W F	Systemic lupus erythematosus	C	6.77	2.18	4.59
47 W M	Acute glomerular nephritis	C	6.64	1.99	4.65
62 W F	?-Systemic lupus erythematosus	C	7.50	2.65	4.85
57 W F	Rheumatoid arthritis	C	6.68	1.71	4.97
17 N M	Rheumatoid arthritis	C	8.42	3.24	5.18
64 W F	Rheumatoid arthritis	C	7.73	2.20	5.53
58 W F	Rheumatoid arthritis	C	7.70	2.11	5.59
42 W M	Active rheumatic heart disease	C	9.22	3.41	5.81
27 W F	Rheumatoid arthritis	C	7.87	2.04	5.83
47 N M	Rheumatoid arthritis	C	8.30	2.46	5.84
21 W M	Acute rheumatic fever	A	7.82	1.86	5.96
59 W F	Systemic lupus erythematosus	C	8.84	2.68	6.16
16 W M	FUO, ?-etiology; probably collagen disease	C	8.44	2.14	6.30
29 N F	Acute rheumatic fever	C	10.24	2.71	7.53
	Sarcoidosis				
32 W F	Sarcoidosis	C	7.50	3.52	3.98
43 W M	Sarcoidosis	LB	7.45	3.47	3.98
30 W M	Sarcoidosis	LB	8.42	4.34	4.08
33 N M	Sarcoidosis	LB	7.36	3.21	4.15
29 N F	Sarcoidosis	B	7.65	3.38	4.27
31 W M	Sarcoidosis	LB	7.56	3.12	4.44
51 W M	Sarcoidosis	LB	7.00	2.39	4.61
40 N F	Sarcoidosis	LB	7.76	2.65	5.11
47 W F	Sarcoidosis	A	8.14	2.96	5.18
31 N F	Sarcoidosis	C	8.25	3.06	5.19
36 N F	Sarcoidosis	B	7.29	2.03	5.26
29 N F	Sarcoidosis	LB	8.41	2.77	5.37
37 W M	Sarcoidosis	LB	9.04	3.44	5.60
37 W F	Sarcoidosis	B	8.49	2.88	5.61
37 W M	Sarcoidosis	C	9.35	2.89	6.45
	Chronic Pulmonary Disease				
35 W M	Bronchiectasis	SP	6.96	3.06	3.90
48 N F	Far-advanced tuberculosis, inactive	C	7.65	3.70	3.95
72 W M	Severe pulmonary emphysema	C	6.96	2.98	3.98
48 W F	Bronchiectasis	SP	2.25	3.24	4.01
84 W F	Pulmonary emphysema and fibrosis	C	5.70	1.67	4.03
65 W M	Empyema	SP	6.50	2.43	4.07

TABLE 2—*Continued*

Age	Race	Sex	Diagnosis	Method of Diagnosis	TP	A	G
Chronic Pulmonary Disease (*continued*)							
58	N	M	Far-advanced tuberculosis, inactive	C	5.96	1.84	4.12
56	W	M	Severe pulmonary fibrosis	C	6.64	2.43	4.21
21	W	M	Lung abscess, chronic	SP	8.14	3.93	4.21
38	N	M	Chronic granulomatous pneumonitis	SP	6.77	2.53	4.24
68	N	M	Multiple pulmonary infarcts	A	6.15	1.84	4.27
50	W	M	Empyema	SP	8.07	3.75	4.32
49	W	M	Bronchiectasis	C	6.24	1.88	4.36
38	W	M	Chronic pneumonitis	SP	8.18	3.81	4.37
60	W	F	Severe pulmonary fibrosis	C	6.96	2.46	4.50
35	W	F	Kyphoscoliosis; pulmonary fibrosis	C	7.05	2.24	4.81
70	W	M	Far-advanced tuberculosis, inactive	C	7.87	3.01	4.86
65	W	F	?-Hamman-Rich syndrome	A	6.82	1.77	5.05
31	W	M	Bronchiectasis	SP	7.82	2.17	5.11
58	W	M	Multiple bronchiectatic abscesses	SP	7.82	2.55	5.27
63	W	F	Severe pulmonary fibrosis	C	7.45	2.09	5.32
47	W	M	Chronic lung abscess	SP	6.96	1.54	5.42
75	W	M	Far-advanced tuberculosis, inactive	C	7.60	2.18	5.42
Infectious Diseases							
60	W	F	Cellulitis of leg, ? erysipelas	C	6.68	2.70	3.90
78	N	F	Typhoid abscess in neck	SP	7.05	3.14	3.91
69	W	M	Pneumococcal pneumonia	C	7.05	3.13	3.92
28	W	M	Subacute bacterial endocarditis	C	6.68	3.75	3.93
46	W	M	Tuberculous pericarditis	C	6.36	2.43	3.93
57	W	F	Epidural abscess	SP	6.86	2.90	3.96
35	N	F	Syphilis, with aortitis	C	7.35	3.38	3.97
45	N	F	Bronchopneumonia	C	8.50	3.52	3.98
57	W	M	Bilateral cavitary tuberculosis	C	5.86	1.86	4.00
16	N	M	Congenital syphilis; ant. uveitis	C	7.50	3.50	4.00
58	N	F	Acute pneumonitis	C	6.36	2.36	4.00
43	W	M	Staphylococcal septicemia	A	5.54	1.54	4.00
67	W	M	Lobar pneumonia	C	6.86	2.85	4.01
43	W	M	Active RUL tuberculosis	C	6.53	2.51	4.02
61	W	M	Viral pneumonitis	C	7.16	3.14	4.02
37	W	M	Retroperitoneal abscess, ?-etiology	SP	6.46	2.43	4.03
47	W	M	Tuberculous empyema	C	7.23	3.17	4.06
27	N	M	Bronchopneumonia	C	7.40	3.33	4.07
20	W	F	Acute pyelonephritis	C	7.30	3.22	4.08
67	N	F	Bronchopneumonia	C	6.33	2.24	4.09
46	W	M	Multiple decubiti; osteomyelitis	C	6.50	2.39	4.11
29	N	M	Lobar pneumonia	C	7.35	3.20	4.15
66	N	M	Miliary tuberculosis	A	6.64	2.48	4.16
58	W	M	Pneumococcal pneumonia	C	6.82	2.65	4.17
62	W	F	Ulcerative colitis; *E. coli* septicemia	C	6.86	2.68	4.18
44	W	M	Ulcerative colitis with fistulae	SP	6.49	2.30	4.19
68	W	M	Osteomyelitis of toe	C	6.58	2.39	4.19
78	N	M	Thrombophlebitis	C	7.45	3.24	4.21
42	W	M	Pneumococcal meningitis	C	5.78	1.56	4.22
30	W	M	Regional ileitis with abscesses	SP	6.15	1.93	4.22
15	W	M	Cerebellar abscess	A	7.45	3.22	4.23
43	W	M	Pulmonary tuberculosis, active	C	7.01	2.77	4.24
65	N	M	Bronchopneumonia	C	7.30	3.06	4.24
63	N	M	Miliary tuberculosis	A	6.86	2.61	4.25
56	W	F	Bilateral renal tuberculosis	C	6.64	2.36	4.28
41	W	M	Ulcerative colitis with fistulae	SP	6.53	2.13	4.40
84	W	F	Bronchopneumonia	C	7.50	3.09	4.41

TABLE 2—*Continued*

Age Race Sex	Diagnosis	Method of Diagnosis	TP	A	G
	Infectious Diseases (*continued*)				
62 W M	Bronchopneumonia	C	6.77	2.36	4.41
33 N M	Tuberculous lymphadenitis	SP	7.20	2.74	4.42
40 N F	Acute pyelonephritis	C	7.35	2.85	4.50
36 N M	Far-advanced active tuberculosis	C	6.28	1.77	4.51
46 N F	Resolving pneumonitis	C	7.50	2.98	4.52
41 N M	Pulmonary tuberculosis	SP	7.65	3.09	4.56
56 W M	Tertiary syphilis, untreated	C	7.63	3.04	4.59
58 W M	Multiple decubiti (multiple sclerosis)	C	6.50	1.91	4.59
63 W M	Primary atypical pneumonia	C	6.82	2.22	4.60
62 W M	Active syphilis; pneumonia	C	6.42	1.75	4.67
31 W F	Subacute bacterial endocarditis	C	7.10	2.43	4.67
88 W M	Focal pneumonitis	A	6.82	2.14	4.68
54 W M	Bilateral cavitary tuberculosis	SP	7.20	2.51	4.69
39 N F	Pulmonary tuberculosis; diab. mellitus	C	6.07	1.35	4.72
56 W M	Bronchopneumonia; active syphilis	C	7.70	2.98	4.72
66 W M	Bronchopneumonia	C	7.80	3.06	4.76
70 N F	Untreated tertiary syphilis	C	6.74	1.77	4.92
17 W M	Osteomyelitis of pelvis (paraplegia)	C	7.92	2.86	5.06
25 N M	Acute brucellosis suis	C	7.65	2.41	5.24
70 W M	Bronchopneumonia	C	7.00	1.66	5.34
48 N F	FUO with arthralgia, ? etiology	C	8.84	2.65	6.19
45 N M	Tuberculous peritonitis	C	8.98	2.43	6.55
22 N F	Subacute bacterial endocarditis	C	9.28	2.61	6.67

2. The only marked globulin elevations in the carcinoma groups occurred in patients with metastatic carcinoma, and about two thirds of all these "metastatic carcinoma" cases had obvious liver involvement.

3. There appeared to be no correlation between the globulin values and the primary site and histology of the tumors, whether localized or metastatic.

4. The occurrence of seven cases in which lymphomata were the cause for hyperglobulinemia was of interest, since this etiology for the protein elevation is not generally appreciated, although it has been observed by others.[17, 18, 19]

5. Of the infectious disease cases, a sizable number had either active tuberculosis, syphilis or pneumonia. Others were associated with suppuration. The two highest globulin values in this set of cases are seen in a patient with subacute bacterial endocarditis (6.67 gm.%), and in another with tuberculous peritonitis (6.55 gm.%). The occurrence of marked globulin elevation in both of these conditions has been described.[50, 57] Also of note is the presence of marked hyperglobulinemia (5.24 gm.%) in a patient with acute brucellosis. This has been subsequently observed in two other patients with acute brucellosis seen at this hospital who are not reported in the present series.

Table 3 * shows those "unclassified" cases in which no specific "hyper-

* The listing of cases in order of ascending globulin values—as in table 2—was not strictly followed here, in order to keep similar diagnoses adjacent to each other in the tabulation.

TABLE 3

"Unclassified" Cases. Diagnoses and Serum Protein Data in Patients Not Having Specific "Hyperglobulinemic" Disease
(Abbreviations are used as indicated in Table 2)

Age Race Sex	Diagnosis	Method of Diagnosis	TP	A	G
	Chronic Renal Disease				
84 W M	Arteriolar nephrosclerosis; anemia	C	6.33	2.32	4.01
67 W M	*Arteriolar nephrosclerosis	C	7.16	2.98	4.18
50 N F	Arteriolar nephrosclerosis; malignant hypertension	A	7.20	2.36	4.84
58 W F	Arteriolar nephrosclerosis; HCVD	A	7.96	2.74	5.22
67 N M	Arteriolar nephrosclerosis; HCVD	C	7.16	1.93	5.23
19 W F	Chr. and acute pyelonephritis	C	7.65	3.70	3.95
78 W F	Chr. pyelonephritis	A	7.56	3.50	4.06
58 W M	*Chr. pyelonephritis; l. nephrectomy	C	7.40	3.20	4.20
68 W M	Chr. pyelonephritis; suprapubic cystostomy	C	6.33	2.09	4.24
66 W F	*Chr. pyelonephritis; paraplegia	A	6.15	1.88	4.27
57 W F	Chr. pyelonephritis; staghorn calculi	C	7.50	3.06	4.44
36 W M	Chr. and acute pyeloneph.; r. renal stone	C	5.82	1.37	4.45
50 W M	Chr. pyelo.; renal stones	C	8.42	3.50	4.92
61 W F	*Chr. pyelo.; ASHD and HCVD	A	7.45	2.24	5.21
45 W M	Nephrolithiasis with nephrolithotomy	S	7.60	3.65	3.95
51 W M	Renal stones; acute gouty arthritis	C	7.82	3.84	3.98
43 N F	Renal stones; ? etiology	C	7.70	3.55	4.15
57 W F	Nephrolithiasis 2° to alkali intake	S	7.35	3.20	4.15
44 W M	Bilat. staghorn calculi	S	7.50	3.20	4.30
66 W M	Bilat. staghorn calculi; ASHD	C	7.30	2.90	4.40
56 W M	Renal stones	C	7.87	3.30	4.57
34 W F	*Kimmelstiel-Wilson syndrome	C	6.20	3.18	4.02
60 W F	*Kimmelstiel-Wilson syndrome	C	5.82	1.80	4.02
32 W M	*Kimmelstiel-Wilson syndrome; encephalomalacia	C	6.72	2.68	4.04
73 W M	*Kimmelstiel-Wilson syndrome	C	6.36	2.27	4.09
56 W M	*Kimmelstiel-Wilson syndrome	C	5.66	1.42	4.42
2 W F	Cong. megalo-ureter; ureteroneocystostomy	S	6.90	2.98	3.92
5 W F	Extrophy of bladder; ureterosigmoidostomy	S	7.50	3.52	3.98
5 W F	Cong. hydro-ureter; ureteroneocystostomy	S	7.87	3.84	4.03
64 W M	Chronic nephritis; ? etiology; chronic gout	C	6.86	2.96	3.90
45 W M	Poisoning (? mercury) of unknown origin	C	6.19	2.20	3.99
44 W M	Multiple renal abscesses; ? etiology	P	7.00	2.90	4.10
58 W F	Azotemia; ? etiology	C	7.65	3.47	3.18
	Cardiac Disease				
50 W M	IRHD; loculated pleural effusion	C	7.05	3.21	3.93
38 W F	IRHD; cardiac decompensation; no edema	C	7.60	3.64	3.96
55 W F	IRHD; in for valvuloplasty	C	7.35	3.33	4.02
43 W F	IRHD; in for valvuloplasty	C	7.35	3.30	4.05
55 W F	IRHD; senility due to CVAs	C	7.70	3.27	4.43
30 W F	IRHD; in for evaluation of status	C	8.37	3.47	4.90
63 W F	ASHD; myocardial infarction	C	7.11	3.20	3.91
59 W M	ASHD; myocardial infarction	C	7.65	3.52	4.13
61 W M	ASHD; myoc. infarct.; cardiac decomp.	C	7.45	3.12	4.33
83 W M	HCVD, in compensation	C	7.10	3.20	3.90
57 W F	HCVD; asymptomatic cholelithiasis	C	7.76	3.84	3.92
48 N F	HCVD; decompensated, edema, ascites	C	6.42	2.43	3.99
43 W F	Essential vascular hypertension	C	7.45	3.41	4.04
57 W F	*HCVD, compensated; cholelithiasis	C	5.90	1.71	4.19
66 W F	HCVD; genl. A-S	C	7.50	3.12	4.38

TABLE 3—*Continued*

Age Race Sex	Diagnosis	Method of Diagnosis	TP	A	G
	Cardiac Disease (*continued*)				
60 W F	HCVD & ASHD; angina	C	7.50	3.10	4.40
63 W M	HCVD & ASHD, decompensated	C	6.53	2.13	4.40
62 W F	*HCVD; encephalomalacia	C	6.90	2.48	4.42
62 W F	HCVD; arthralgia 2° to Apresoline	C	8.06	3.61	4.43
39 W M	Heart disease, ? etiology	C	6.77	2.83	3.94
12 N M	Tetral. of Fallot; retarded growth	S	8.54	3.75	4.79
	Arteriosclerosis Obliterans, Additional Diagnoses as Indicated				
76 W M	ASHD; in for leg amputation	C	6.58	2.65	3.93
64 W F	*; Gangrene; ASHD, decompensated	C	7.16	3.20	3.96
49 W M	*; Bilat. amputations; duod. ulcer	C	6.33	2.29	4.04
72 W M	ASHD; in for leg amputation	C	6.77	2.63	4.14
67 W F	*; Gangrene	C	6.58	2.43	4.15
67 W F	*; In for leg amputation	C	6.78	2.65	4.17
65 N F	In for sympathectomy	C	7.29	3.61	4.31
70 W F	*; Gangrene; ASHD; encephalomalacia	C	7.92	2.53	5.39
	Cerebral Syndromes				
57 W M	CVA; HCVD	A	7.07	3.12	3.95
44 W F	Basilar artery thrombosis	A	7.30	3.30	4.00
68 W F	Cerebral A-S; hypertension; O-A	C	6.68	2.68	4.00
67 N M	*; CVA	C	6.82	2.80	4.02
81 W M	Cerebral A-S; parkinsonism; hiat. hern.	C	5.83	1.85	4.03
71 W M	Syncope; ASHD; hemorrhoids	C	6.50	2.46	4.04
28 N M	Acute alcoholism	C	7.56	3.52	4.04
47 N F	*; Dizziness and nausea; cerebral A-S	C	7.50	3.33	4.17
53 N F	*; CVA; ASHD	A	6.58	2.36	4.22
65 N F	Internal carotid art. aneurysm	C	7.30	3.05	4.25
64 W M	Cerebral A-S; parkinsonism	C	7.10	2.85	4.25
89 W F	Cerebral and generalized A-S	C	7.20	2.93	4.27
	Bone and Joint Disease				
73 W F	Osteoarthritis; osteoporosis	C	6.86	2.93	3.93
73 W M	Osteoarthritis; pain in groin	C	7.35	3.27	4.08
61 N M	Osteoarthritis; scoliosis	C	7.82	3.72	4.10
65 W M	Fractured vertebra; osteoporosis	C	7.20	3.09	4.11
64 W F	Osteoporosis; steatorrhea; ASHD	C	8.14	3.57	4.57
51 W M	Fractured vertebrae, traumatic	C	6.90	3.06	3.90
54 W F	Fractured vertebra; osteoporosis	C	8.08	3.72	4.36
63 W F	Fractured hip; IRHD	C	7.76	3.80	3.96
74 W F	Fractured hip; generalized A-S	C	7.05	3.04	4.01
72 W F	Fractured hip; multiple pulm. infarcts	C	5.86	1.50	4.36
56 W M	Fractured radius, traumatic	C	6.77	2.85	3.92
74 W M	Fractured parietal bone	A	5.90	1.86	4.04
66 W F	Herniated intervertebral disc	C	7.60	3.23	4.53
59 W F	Lytic lesion in pubis, ? etiology	C	8.14	3.20	4.94

TABLE 3—*Continued*

Age Race Sex	Diagnosis	Method of Diagnosis	TP	A	G
	Neuromuscular Disease				
45 W M	Pain in groin, ? etiology	C	7.40	3.33	4.07
59 W F	Progressive muscular dystrophy	B	7.50	3.38	4.12
60 W F	Paralyzed l. diaphragm, ? etiology	C	7.40	3.24	4.16
74 W F	*; Diabetic neuropathy; hypertension	C	6.53	3.32	4.31
47 W F	Undiagnosed neuromuscular disease	C	7.92	3.20	4.72
	Nutritional Problems				
57 W M	Burn; chronic alcoholic	C	6.42	2.41	4.01
23 W M	Burn (24 days after admission)	C	7.56	3.44	4.12
53 W M	Cholecystectomy wound dehiscence, with electrolyte problems	C	6.84	2.90	3.94
31 W F	Multiple fractures and skin trauma	C	6.07	2.09	3.98
48 W M	Cyst of septum pellucidum, postop.	S	6.64	2.65	3.99
22 W F	Postop. debilitation with decubiti	C	7.35	3.04	4.31
36 W M	Multiple sclerosis, debilitated	A	6.12	1.88	4.24
87 W F	Dehydration; partial intest. obstruc.	C	6.82	2.55	4.27
49 W M	Dehydrated; duodenal ulcer	C	8.08	3.79	4.29
57 W M	Debilitated; achalasia of esophagus	S	6.64	1.84	4.80
26 W F	Chron. gastric fistula; subdiaph. abscess	S	7.92	3.01	4.91
	Skin Diseases				
71 W F	Pemphigus; generalized A-S	C	7.30	3.24	4.06
73 W M	Exfoliative dermatitis	C	7.10	2.72	4.38
45 W F	Dermatitis, ? seborrheic, ? herpetiform	C	7.76	3.19	4.57
20 N F	Chronic neurodermatitis	C	8.25	3.52	4.73
	Miscellaneous				
59 W F	Thyrotoxicosis	C	7.40	3.44	3.96
49 W F	Thyrotoxicosis	C	7.18	2.98	4.20
31 W F	Myxedema	C	7.70	3.61	4.09
50 N F	Microcytic anemia, ? etiology	C	8.18	3.93	4.25
82 W F	Microcytic anemia; diverticulosis	C	6.58	2.24	4.34
73 W M	Nutritional anemia	C	6.42	1.86	4.56
26 W F	Ruptured ectopic pregnancy	C	8.25	4.31	3.94
35 N F	Toxemia of pregnancy	C	7.10	3.14	3.96
26 N F	Toxemia of pregnancy	C	7.87	3.41	4.46
60 W M	Prostatism; duodenal ulcer	C	6.72	2.72	4.00
22 W F	*; In for cosmetic eye enucleation	C	7.70	3.67	4.03
47 N F	*; Bronchial asthma	C	7.61	3.57	4.04
78 W F	Varicose veins; ASHD	C	7.20	3.16	4.04
47 N F	Chronic cystic mastitis	B	7.56	3.47	4.09
62 N M	Undiagnosed abdominal disease	C	7.56	3.33	4.23
38 N F	Uterine fibromyomata	SP	7.16	2.89	4.27
68 W M	Retroperitoneal bleeding, ? etiology	S+P	7.50	2.29	5.21
41 W F	*; Taking too much insulin	C	7.30	3.06	4.24

globulinemic" disease could be found, and demonstrates the diversity of clinical pathology which may be associated with an elevated serum globulin. This table shows that:

1. A large number of patients had chronic renal disease, of varying etiology, some with associated diabetes mellitus. Hyperglobulinemia in renal disease has been noted by Kumpf [45] and others, although no globulin elevations were found in 24 terminal renal disease patients studied by Peters et al.[58] It should be noted that serum globulin values higher than 5.00 gm.% were found in only five patients in the entire "unclassified" group; of these, three had chronic renal disease.

2. Another large segment of patients had some variety of heart disease. Globulin elevations associated with heart disease have been described by Payne and Peters [59] and also by Kumpf.[45]

3. Of those patients with arteriosclerosis obliterans and hyperglobulinemia, two thirds had diabetes mellitus.

4. Injury reactions as a cause of hyperglobulinemia, as seen in the number of patients listed here with bone fractures, burns or other trauma, have been described by Cuthbertson and Tompsett [60] and others.

5. Hyperglobulinemia was present in four patients with skin disorders. Lever [61] has made similar observations.

6. Almost one-half of all the "unclassified" cases had debilitation or malnutrition secondary to either senility, chronic illness or surgical procedures. The rôle of these phenomena in the production of hyperglobulinemia has been discussed in several papers.[62-66]

7. Finally, a number of patients had an elevated globulin which defied further explanation. It is entirely possible that these patients had other diseases, but on the basis of the data obtained in the hospital no further diagnoses could be made.

The albumin and globulin values from tables 2 and 3 were then used as coördinates for points on a scatter-graph (not shown here) in which each point represented an individual case and was marked with an appropriate diagnostic symbol. On visual inspection of this graph it was apparent that the "unclassified" cases were most prevalent in that area where globulin was less than 4.2 gm. per 100 ml., while very few of these "unclassified" patients were present in the group with globulin values above 5.0 gm. per 100 ml. These values thus seemed natural boundary lines for three groups of globulin ranges, created as follows:

Group	Globulin Range (gm. per 100 ml.)
A	3.90–4.20
B	4.21–4.99
C	5.00 and higher

The types of cases found in these three globulin zones were then considered, and their distribution by diagnostic categories is listed in table 4.

TABLE 4

Distribution of Case-Diagnoses in Each of the Globulin Groups

NOTE: The percentages refer to the number of cases with a given diagnosis in each globulin group as a fraction of the total number of cases in that group.

		Liver Disease*	Neoplastic Disease†	Lymphomas	Multiple Myeloma	Sarcoidosis and Collagen Disease	Chronic Pulmonary Disease	Infectious Diseases	Unclassified	Total
Group A: Globulin Values 3.90–4.20 gm. %	No. of cases	14	28	1	2	13	7	27	74	166
	Percentage of this group	8.4	16.8	0.6	1.2	7.9	4.3	16.3	44.5	100.0
Group B: Globulin Values 4.21–4.99 gm. %	No. of cases	33	34	2	2	13	10	27	47	168
	Percentage of this group	19.6	20.2	1.2	1.2	7.7	6.0	16.1	28.0	100.0
Group C: Globulin Values 5.00 gm. % and higher	No. of cases	11	2	4	8	18	6	6	5	60
	Percentage of this group	18.3	3.3	6.7	13.3	30.0	10.0	10.0	8.4	100.0
Total for the entire series	No. of cases	58	64	7	12	44	23	60	126	394
	Percentage of the total	14.7	16.3	1.8	3.0	11.2	5.8	15.3	32.0	100.0

* Combines the categories of "Laennec's Cirrhosis" and "Other Liver Diseases" listed in table 2.
† Combines the categories of "Nonmetastatic Cancer" and "Metastatic Cancer" listed in table 2.

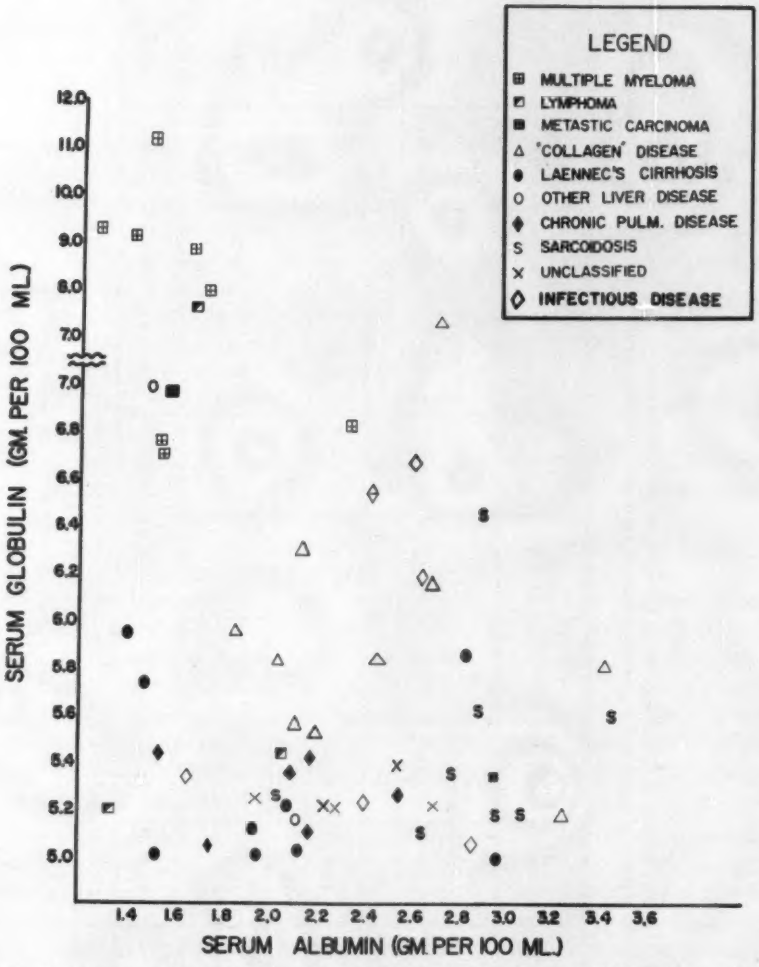

FIG. 1. Albumin-globulin relationships and diagnostic classification of 60 patients with serum globulin values of 5.00 gm. per 100 ml. or higher.

Note that this table shows the total number of all types of cases found in each globulin group, and indicates the percentage of these cases occupied by patients in a given diagnostic category. It may be seen that, of the entire series of 394 cases, 126 (32.0%) had diseases not specifically associated with hyperglobulinemia. Seventy-four of these "unclassified" cases were found in Group A, comprising 44.5% of the 166 cases in that group. As the higher globulin ranges were entered, this percentage decreased to 28.0% in Group B and 8.4% in Group C. On the other hand, the com-

bination of patients with multiple myeloma, sarcoidosis and collagen disease made up only 9.1% of the patients in Group A, and 8.9% in Group B, but comprised 43.3% of the 60 patients in Group C. Thus, in patients with a serum globulin of 5.00 or higher, the chances of having a specific "hyperglobulinemic" disease were nine in 10, and of having either multiple myeloma, sarcoidosis or collagen disease, were almost one in two. Of the 168 patients in Group B with moderate but not marked globulin elevation, over one third had liver or neoplastic disease. The other diagnostic categories did not show any remarkable variation in their distribution among the cases of the three globulin zones.

The relative values of serum albumin and globulin and diagnoses in the 60 patients with serum globulin values higher than 5.0 gm. per 100 ml. have been depicted in figure 1. This graph shows a number of points which deserve further comment. The only patients with globulin values of 8.00

TABLE 5

Total Protein and Globulin Values in 394 Cases of Hyperglobulinemia
NOTE: Laboratory range of normal for total protein is 6.30–7.69 gm. per 100 ml.

Total Protein Values (gm. %)	Number of Patients in Globulin Range			Total Number of Patients
	3.90–4.20	4.21–4.99	5.00 and higher	
Less than 6.30	20	25	1	46
6.30–6.99	68	50	4	122
7.00–7.69	69	60	15	144
7.70–8.39	9	30	16	55
8.40 and higher	1	2	24	27

gm.% or higher are cases of multiple myeloma, and of all the myeloma patients in this group, only one had a serum albumin value higher than 2.00 gm.%. The marked hypoalbuminemia frequently seen in this disease has been noted often,[16] and does not frequently correlate with the nutritional status of the patient. No case in this subgroup of 60 patients had a normal serum albumin (3.7 gm.% or higher), and only four had an albumin value greater than 3.00 gm.%. These were two cases of sarcoidosis and two with collagen disease. In general, the right side of the graph, where albumin values are relatively higher, is dominated by patients with sarcoidosis and collagen disease, while the left side, with relative hypoalbuminemia, has a high incidence of liver and neoplastic disease.

Table 5 shows the relationship and distribution of total serum protein and globulin values for the entire 394 patients. The following points are evident:

1. Two hundred sixty-six patients had normal, 46 subnormal, and 82 above-normal values for total serum proteins. Since all of the patients had hyperglobulinemia, this affords ample evidence that an increase in serum globulin is not usually reflected as an increase in total serum protein.*

2. Of the 46 patients with subnormal total protein values, more than half had globulin values higher than 4.20 gm.%. (Most of these patients had Laennec's cirrhosis or metastatic carcinoma.)

3. Of the 266 patients with normal total protein values, more than half had globulin values less than 4.20 gm.%. In these ranges, therefore, the albumin appears to be well preserved.

4. Of the 55 patients with relatively small elevation of total protein, (7.70 to 8.39), 39 had mild to moderate hyperglobulinemia. Closer inspection of the original data (tables 2 and 3) shows that 21 of these 39 patients were "unclassified." The other 16 patients in this total-protein group had marked hyperglobulinemia, and only one of these was an "unclassified" case.

5. Of 27 patients with a total protein value of 8.40 gm.% or higher, only three had a serum globulin of less than 5.00 gm.%. It would seem important, therefore, to suspect the presence of marked hyperglobulinemia when total serum proteins fall in this range.

Discussion

The physiologic and pathologic significance of serum protein components has been considered in a number of reviews.[45, 67-79] For the most part, these have been concerned with the occurrence of hyperglobulinemia in a series of cases of a specific disease. The reverse process—that of studying the disease present in a series of cases of hyperglobulinemia, within different ranges of globulin elevation—has not been hitherto reported with such a large number of patients.

The conditions considered to be specific hyperglobulinemic diseases have been listed in table 1. The table does not include primary systemic amyloidosis [80, 81] (which has at times been described with hyperglobulinemia), since other work [82] indicates that globulin elevation in this disease is found only in association with multiple myeloma. The table also omits the "physiologic" hyperglobulinemia which has occasionally been reported with drug sensitivity reactions.[83, 84]

In addition to these, two other clinical entities have been attributed to hyperglobulinemia. The "purpura hyperglobulinemica" of Waldenström [85] is characterized by an elevated serum globulin, various hematologic abnormalities, and a relatively long course in which no specific pathologic diagnosis

* Conversely, hyperproteinemia is almost always due to hyperglobulinemia. Since the latter property, however, was the criterion of selection for the cases in this study, we have no data on possible cases with normal globulin values, where a marked serum albumin elevation might account for hyperproteinemia.

is established. Other authors [86-89] have also described such cases. Bing et al.[90-92] have reported a different series of patients, with no specific diagnosis and diverse neurologic disorders associated with a high serum globulin. No case of either of these two types was recognized in the present series. Close examination of the case reports in the Waldenström and Bing series suggests that some of these may have had lymphomas, sarcoidosis or systemic lupus erythematosus, in which the necessary diagnostic tests were not available or could not be done at the time the patients were seen. Hematologic abnormalities have now been often reported in sarcoidosis,[34, 93, 94] and lupus has become notorious for its associated neurologic abnormalities,[95] its sometimes prolonged clinical course,[24] and its frequent early masquerade solely as purpura.[96] The recent development of accurate diagnostic tests for these clinical entities may permit their being recognized more frequently in present-day patients with hyperglobulinemia of obscure etiology, although an occasional rare case may remain unexplained.

In any correlation of serum globulin values with disease states, preliminary consideration must be given to extraneous factors which can alter globulin results, either directly or by their effect on total protein or albumin values. Most prominent among these are methods for the collection [97] and analysis of the serum. It has already been mentioned, for example, that lipemic sera will give falsely high total protein results if measured by the biuret method, and that other sera may give falsely low globulin values if fractionated by the Howe method. In addition, there are various physiologic factors which can change serum protein components. Peters and Van Slyke [98] point out the effects of previous hydration, body temperature and hyperventilation, and Dyson [99] has made a survey of age, sex and occupational factors. Malnutrition, fever, injury, dehydration and edema have all been considered in other investigations.[62-66, 100] (Actually, many of these physiologic factors affect mainly albumin, and alter globulin only secondarily.)

Certainly in the variety of diseases in the "unclassified" group (table 3), the physiologic factors just noted, rather than the disease state, may account for many of the serum globulin elevations. To a lesser extent, this could also be true in many of the cases listed in table 2 as specific "hyperglobulinemic" diseases. However, the clinician, confronted by an elevated serum globulin, can easily determine whether dehydration, fever, malnutrition or a laboratory error exists. But these do not answer the question: Does this patient have multiple myeloma, sarcoidosis or some other disease? For this reason, only the ultimate clinical diagnoses have been considered in this survey, exclusive of pathophysiologic variations. Within the limitations of the clinical material seen in a general hospital in the New England area, and the methods used in its analysis, the data would appear valid for assessing the utility of this laboratory test as a diagnostic tool.

Examination of the results leads to the conclusion that a serum globulin

of 5.00 gm. per 100 ml. or higher is usually of diagnostic significance. Ninety per cent of these patients had specific "hyperglobulinemic" disease, of which one-half were either multiple myeloma, collagen disease or sarcoidosis. In this group of patients, therefore, thorough laboratory and clinical evaluation is certainly indicated if the diagnosis is not otherwise evident. A much greater problem is presented by patients with mild globulin elevations (from 3.9 to 4.2 gm. per 100 ml.). Although many of them were seriously ill, 50% did not have a disease commonly associated with hyperglobulinemia, and only one in 12 had either multiple myeloma, collagen disease or sarcoidosis. The extent of further diagnostic procedures in these patients will depend on clinical judgment, and each case should be determined on its own merits. It is entirely possible, of course, that a few of these cases are in the "prodromal" stage of some "hyperglobulinemic" disease in which the diagnosis cannot be made until some later date. A careful, long-term follow-up would be necessary to establish this concept.

In the intermediate hyperglobulinemia range (4.2 to 5.0 gm. per 100 ml.), the incidence of multiple myeloma, sarcoidosis and collagen disease was not greater than that found in the zone of borderline elevation (3.9 to 4.2 gm. per 100 ml.). However, the intermediate zone contained appreciable numbers of patients with liver disease, cancer, and acute and chronic inflammations. The laboratory pursuits are thus likely to be productive when a patient with a globulin value in this group has not had a diagnosis established, although the latter diagnoses are more apt to be obvious on clinical grounds alone, and thus to require less extensive laboratory tests.

Although only two thirds of the 394 patients in this series had "specific" disorders, the others all had some demonstrable organic disease. Measurement of the serum globulin has some value, therefore, as a screening test to separate functional from organic pathology. The total protein determination [101] alone would not serve this purpose, since an elevated serum globulin often occurs in the presence of a normal serum total protein value. It may be, however, that simpler laboratory procedures, such as the erythrocyte sedimentation rate or the formol gel test,[102, 103] would be less expensive as screening methods.

Because of expanded laboratory facilities, growing interest in electrophoretic correlations, and other reasons cited at the beginning of this paper, the determination of serum total protein with albumin-globulin partition has been made with increasing frequency at many medical centers. At the New Haven Hospital, for example, 2,904 total protein with albumin globulin measurements were done in 1953. This has produced a large volume of laboratory data and created the problems of interpreting them, particularly since the finding of hyperglobulinemia can imply the existence of serious disease entities. From the analysis reported here, it can be concluded that the TP with A/G measurement, in addition to its value as an index of

nutritional and other states, has distinct diagnostic correlations when the globulin results are sufficiently high and are carefully interpreted. Whether these correlations occur often enough to warrant continued general use of this measurement as a *diagnostic* test, or whether it can be more conveniently replaced for this purpose by quantified paper electrophoresis technics, are problems to be evaluated and answered by the individual medical services involved.

Summary

1. The hospital records of a series of 394 patients with hyperglobulinemia have been analyzed.

2. Of these, 268 patients had diseases generally associated with an elevated serum globulin, viz., multiple myeloma, sarcoidosis, collagen disease, liver disease, cancer, chronic pulmonary disease and certain infections.

3. The remaining 126 cases could not be placed in any of the above diagnostic categories and were termed "unclassified."

4. In patients whose serum globulin was 5.0 gm. per 100 ml. or higher, over 90% had specific "hyperglobulinemic" diseases; about half had either multiple myeloma, sarcoidosis or collagen disease.

5. In patients with only slightly elevated serum globulin values (3.9 to 4.2 gm. per 100 ml.), almost one half were in the "unclassified" category. The incidence of "unclassified" cases decreased in the intermediate ranges (4.2 to 5.0 gm. per 100 ml.) of globulin elevation.

6. Only about 20% of patients with hyperglobulinemia also exhibited hyperproteinemia.

7. The implications of these data are discussed with reference to the use of the albumin-globulin measurement as a diagnostic aid.

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Summario in Interlingua

Pro determinar le signification del isolate constatation laboratorial de elevate nivellos del globulina seral, le protocollos hospitalari de 394 patientes con nivellos de globulina seral de 3,9 g pro cento o plus esseva analysate. Le valor de 3,9 g pro cento esseva seligite como criterio de inclusion del casos individual proque illo es le limite superior del spectro normal secundo le methodo de Cohn e Wolfson. Esseva constatate que le 394 patientes del serie total includeva 268 casos de morbos in que le presentia de hyperglobulinemia es frequentemente reportate, i.e. myeloma multiple, morbo collagenic, chronic morbo pulmonar, cirrhosis e altere morbos hepatic, e certe infectiones de character chronic. Del altere latere, le resto del patientes, representante un serie de 126 casos, manifestava un grande varietate de disordines que non se associa communmente con nivellos excessive de globulina seral, i.e., per exemplo, morbos del systemas cardiovascular, renal, endocrin, e musculo-squeletal. Tamen, le serie includeva nulle patiente sin significative morbo organic.

Le examine plus detaliate del datos in gruppos de comparabile grados de augmento in le nivellos del globulina seral resultava in le sequente constatationes. Inter 60 patientes con nivellos de 5,0 g pro cento o plus de globulina seral, il habeva 30 casos de myeloma multiple, sarcoide, e morbo collagenic, e omne le 60, con cinque exceptiones, habeva morbos que es communmente associate con hyperglobulinemia. In un secunde gruppo de 168 patientes con nivellos de globulina seral de inter 4,2 e 5,0 g pro cento, le majoritate habeva diagnoses de morbo hepatic, malignitate metastatic, e chronic difficultates pulmonar, durante que solmente paucos habeva myeloma multiple, morbo collagenic, a sarcoide. In contrasto con iste constatationes, quasi 50 pro cento del patientes con elevationes liminal del globulina seral, i.e. con nivellos infra 4,2 g pro cento, manifestava un grande varietate de "non-classificate" morbos chronic in un o plure systemas organic. Iste factos pare indicar que levemente elevate nivellos de globulina seral es multo restringite in lor signification diagnostic. Del altere latere, marcate augmentos de iste fraction de proteina seral indica frequentemente le presentia de un specific processo pathologic.

Il es interessante notar que solmente 20 pro cento del patientes con hyperglobulinemia exhibiva etiam le presentia de hyperproteinemia. Isto significa que le majoritate del mentionate conditiones pathologic es associate con un reduction del fraction sero-albuminic. Exceptiones ab iste regula esseva le patientes con sarcoidosis e morbo collagenic. In illes le nivellos de albuminas esseva proxime al norma, mesmo in le presentia de marcate grados de hyperglobulinemia.

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THE CLINICAL SIGNIFICANCE OF HYPERGLOBULINEMIA. II. CORRELATION WITH LIVER FUNCTION TESTS, SEROLOGIC TESTS FOR SYPHILIS, AND BONE MARROW EXAMINATIONS *

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In a previous paper [1] we discussed the selection and clinical analysis of a series of 394 patients with hyperglobulinemia. The present paper considers the results of liver function tests, serologic tests for syphilis, and bone marrow examination in this group of patients.

Liver Function Tests

Materials and Methods

The laboratory of this hospital routinely performs cephalin-cholesterol flocculation, thymol flocculation, thymol turbidity, and alkaline phosphatase tests on all sera sent to it for "liver function tests," unless otherwise specified by the physician. Bromsulphalein retention is measured whenever the dye has been administered. Other samples are often tested for alkaline phosphatase alone. The sera are tested by the methods indicated in the following references: cephalin-cholesterol flocculation,[2, 3] thymol flocculation,[4] thymol turbidity,[4] alkaline phosphatase [5] and Bromsulphalein retention.[6] The selection and diagnostic classification of the patients considered in this study and the methods for measuring serum albumin and globulin have been described previously.[1] Liver function tests and an albumin-globulin value in a given patient were considered to coincide if they were done on the same day, or if the interval between them consisted of only a few days in which it was clear that no change in the clinical status of the patient had occurred. (For example, in a number of patients the incidental finding of hyperglobulinemia on one day was followed by the measurement of liver function on the next day, or several days later. Occasionally, liver function tests preceded the serum albumin-globulin partition by one or more days. The two sets of determinations were considered to be simultaneous only if there had been no change in the patient's status during the interval.)

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In each instance where liver function tests were done, a single set of results was chosen as representative, and the corresponding albumin-globulin values were recorded. These A/G values then served as coördinates on a graph in which albumin values were abscissa, and globulins were ordinate, as shown in figure 1. The graph was broken into four zones by a horizontal line at an arbitrarily chosen globulin value of 4.60 gm.% (to separate mod-

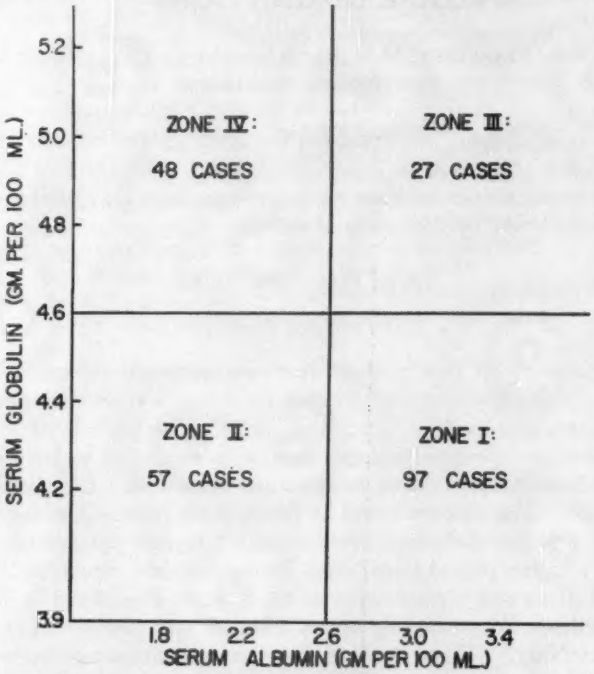

FIG. 1. Distribution of patients with hyperglobulinemia (and liver function tests) in regional zones determined by albumin-globulin values.

Zones I and II are horizontally bounded by serum globulin values of 3.9 and 4.6 gm. per 100 ml., while zones III and IV are occupied by all patients with globulin values of 4.6 gm. per 100 ml. or higher. (Note that the upper limit of normal for serum globulin in this laboratory is 3.9 gm. per 100 ml.) Almost all of these patients had hypoalbuminemia, since the lower limit of normal for serum albumin is 3.7 gm. per 100 ml. The albumin value of 2.60 gm. per 100 ml. serves to separate patients in zones I and III, where the depression of albumin is mild, from those in zones II and IV, where the hypoalbuminemia is more marked.

The number of cases listed in each zone refers to the number of patients with albumin-globulin values in this range who had had liver function tests done.

erate from marked globulin elevations), and by a vertical line at an arbitrarily chosen albumin value of 2.60 gm.% (to provide a division about midway in the numerical range of albumin data available in this series of patients).

Each liver function test was then considered for normality. The range of normal for this laboratory is as follows:

Cephalin-cholesterol flocculation: Less than or equal to 1 plus in 24 hours, and to 2 plus in 48 hours.

Thymol flocculation: Less than 1 plus.

Thymol turbidity: Less than or equal to 4 units.

Alkaline phosphatase: Less than or equal to 8.6 Bodansky units.

Bromsulphalein retention (45 min.): Less than or equal to 8.0 per cent.*

Each liver function result was then marked, using these criteria, as either normal or abnormal, without specifying the degree of abnormality. The cephalin test was considered abnormal if either the 24- or the 48-hour reading was abnormal, and the thymol test was considered abnormal if either the flocculation or turbidity was out of the normal range.

The patients were then classified according to the diagnostic criteria described in our previous paper. This included a series of specific "hyperglobulinemic" diseases, viz., multiple myeloma, sarcoidosis, collagen disease, liver disease, chronic pulmonary disease, cancer, and certain infectious diseases, in addition to an "unclassified" group. For purposes of the present analysis the patients were divided into two groups: those who had definite liver disease, and those whose diseases are not generally considered hepatic. This diagnostic distinction was made to bring out the relation of albumin-globulin values to liver function tests in those diseases which usually do not produce hepatic parenchymal damage. To preserve the clarity of distinction between hepatic and nonhepatic diseases, this study discarded all cases of metastatic carcinoma, lymphoma and primary hepatic neoplasia. This is because liver involvement is possible, even when not clinically evident, in patients with metastatic carcinoma and lymphomas, and also because the diagnosis of "primary" tumors in the liver rested almost entirely upon biopsy evidence, which could not rule out the possibility that these lesions represented metastatic disease.

With these groups eliminated, the category of "liver disease" thus included all patients with a primary parenchymatous disease, or with distinct hepatic disease secondary to pathology in the pancreatic-biliary system. All remaining patients were classified as "no liver disease." (In this latter group the diagnosis "inflammations" has been used to combine the categories of "infectious disease" and "chronic pulmonary disease," as used in our previous paper.[1])

Results

There were 57 patients with liver disease, all of whom had measurements of cephalin, thymol and alkaline phosphatase reactions. Of these patients, 36 were diagnosed as Laennec's cirrhosis and 21 had other forms of hepatic disease. In the group without liver disease, 160 patients had cephalin and

* The value actually considered normal by the laboratory is 6.0%. We chose the somewhat higher figure to allow more distinct differentiation of results.

TABLE 1

Number of Normal Cephalin-Cholesterol Test Results in Patients with Hyperglobulinemia

Diagnosis	Zone I Alb.: above 2.6 Glob.: 3.9–4.6	Zone II Alb.: below 2.6 Glob.: 3.9–4.6	Zone III Alb.: above 2.6 Glob.: above 4.6	Zone IV Alb.: below 2.6 Glob.: above 4.6	Total	Per Cent
"Unclassified"	20/32	5/12	3/5	1/4	29/53	54.7
Multiple myeloma and nonmetastatic cancer	6/6	3/8	1/1	4/7	14/22	64.6
Inflammations	10/20	5/15	2/5	3/12	20/52	38.4
Sarcoidosis and collagen disease	2/10	2/7	3/10	3/6	10/33	30.3
Total nonhepatic disease	38/68	15/42	9/21	11/29	73/160	45.6
Percentage normal in nonhepatic disease	55.8	35.7	42.8	37.9	45.6	—
Total liver disease	10/17	2/15	1/6	0/19	13/57	22.8
Percentage normal in liver disease	58.8	13.3	16.6	0	22.8	

In tables 1 through 4 the diagnostic categories are listed as described in the text. The "Zone" files refer to the zones indicated in figure 1. In each of the tabular fractions the denominator refers to the number of patients in whom the test had been done, and the numerator indicates how many of the results were normal. Only one result for a given test was used for each patient, even though the test may have been repeated on several occasions.

thymol tests and 172 had alkaline phosphatase determinations. The Bromsulphalein retention was measured in 46 of the liver disease cases and in 99 of the nonhepatic disease cases.

The relationships among the diagnostic categories, liver function tests and albumin-globulin values are shown in tables 1 through 4.

TABLE 2

Number of Normal Thymol Test Results in Patients with Hyperglobulinemia

Diagnosis	Zone I Alb.: above 2.6 Glob.: 3.9–4.6	Zone II Alb.: below 2.6 Glob.: 3.9–4.6	Zone III Alb.: above 2.6 Glob.: above 4.6	Zone IV Alb.: below 2.6 Glob.: above 4.6	Total	Per Cent
"Unclassified"	23/32	8/12	3/5	1/4	35/53	66.0
Multiple myeloma and nonmetastatic cancer	6/6	4/8	1/1	6/7	17/22	77.2
Inflammations	15/20	14/15	3/5	6/12	38/52	73.0
Sarcoidosis and collagen disease	3/10	2/7	3/10	3/6	11/33	33.3
Total nonhepatic disease	47/68	28/42	10/21	16/29	101/160	63.1
Percentage normal in nonhepatic disease	69.1	66.6	47.6	55.1	63.1	
Total liver disease	9/17	3/15	0/6	2/19	14/57	24.5
Percentage normal in liver disease	52.9	20.0	0	10.5	24.5	

TABLE 3

Number of Normal Alkaline Phosphatase Results in Patients with Hyperglobulinemia

Diagnosis	Zone I Alb.: above 2.6 Glob.: 3.9–4.6	Zone II Alb.: below 2.6 Glob.: 3.9–4.6	Zone III Alb.: above 2.6 Glob.: above 4.6	Zone IV Alb.: below 2.6 Glob.: above 4.6	Total	Per Cent
"Unclassified"	37/41	12/12	4/5	1/4	54/62	87.0
Multiple myeloma and nonmetastatic cancer	9/9	6/8	1/1	7/7	23/25	92.0
Inflammations	16/20	12/15	5/5	9/12	42/52	80.7
Sarcoidosis and collagen disease	8/10	5/7	10/10	1/6	24/33	72.7
Total nonhepatic disease	70/80	35/42	20/21	18/29	143/172	83.1
Percentage normal in nonhepatic disease	87.5	83.3	95.2	62.0	83.1	—
Total liver disease	8/17	6/15	5/6	4/19	23/57	40.3
Percentage normal in liver disease	47.0	40.0	83.3	21.0	40.3	—

The cephalin-cholesterol flocculation results (table 1) indicate the following:

1. The highest percentage of normal values was found among those patients with "unclassified" disease, nonmetastatic cancer and multiple myeloma. This is in striking contrast to the sarcoidosis and the collagen and inflammatory disease cases, in which the incidence of normal results was much lower.

TABLE 4

Number of Normal Bromsulphalein Retention Results in Patients with Hyperglobulinemia

Diagnosis	Zone I Alb.: above 2.6 Glob.: 3.9–4.6	Zone II Alb.: below 2.6 Glob.: 3.9–4.6	Zone III Alb.: above 2.6 Glob.: above 4.6	Zone IV Alb.: below 2.6 Glob.: above 4.6	Total	Per Cent
"Unclassified"	8/15	1/4	1/5	1/2	11/26	42.3
Multiple myeloma and nonmetastatic cancer	1/1	2/4	1/1	5/5	9/11	81.8
Inflammations	7/18	3/8	1/3	5/11	16/40	40.0
Sarcoidosis and collagen disease	4/7	1/2	5/8	2/5	12/22	54.5
Total nonhepatic disease	20/41	7/18	8/17	13/23	48/99	48.4
Percentage normal in nonhepatic disease	48.7	38.8	47.0	56.5	48.4	—
Total liver disease	2/14	0/12	0/6	0/14	2/46	4.1
Percentage normal in liver disease	14.3	0	0	0	4.1	

2. In Zone I, with relatively high serum albumin values and mild hyperglobulinemia, there was a high percentage of normal results in both hepatic and nonhepatic disease cases.

3. Of the 17 patients in Zone I with liver disease, more detailed inspection of the original data showed that seven had Laennec's cirrhosis, and of these, three had normal cephalin tests, whereas the reaction was negative in seven of the 10 patients with hepatic pathology of other origin.

4. Among the patients who did not have overt liver disease, those whose albumin values were relatively higher (Zones I and III) had a higher percentage of normal cephalin tests, regardless of the serum globulin level.

Table 2, with the thymol results shows that:

1. In patients without liver disease the thymol test has a consistently higher percentage of normal values than the cephalin flocculations. This was true both within the individual disease categories and within the albumin-globulin zones. This phenomenon was not seen in the patients with liver disease, where the two tests gave approximately similar results.

2. Here again, the patients with multiple myeloma and nonmetastatic cancer showed a far greater incidence of normal values than did those with collagen disease and sarcoidosis.

3. Many patients with inflammatory disease had normal thymol tests but abnormal cephalin flocculation tests.

4. Among the patients who did not have overt liver disease, the percentage of abnormal thymol tests was greatest in those with globulins of 4.6 gm.% or higher (Zones III and IV), and the reaction did not appear to reflect serum albumin values as distinctly as its cephalin counterpart.

Table 3 demonstrates that:

1. Alkaline phosphatase values are normal more frequently than cephalin and thymol tests in hyperglobulinemic patients without liver disease. For reasons not apparent on reëxamination of the original data, the patients without liver disease in Zone IV appeared to have fewer normal alkaline phosphatase values than those in other zones.

2. In patients with liver disease, this test also shows a greater incidence of normal values than the other two tests. Separation of the liver disease group into Laennec's cirrhosis and "other liver disease" showed normal phosphatase results in 19 of 36 patients in the former group and in only four of 21 patients in the latter. Since "other liver disease" was often secondary to biliary obstruction, this would account for the more abnormal alkaline phosphatase results found in these cases.

The Bromsulphalein retention data are given in table 4. It may be seen that:

1. A significant number of abnormal values are found in the patients who were not thought to have liver disease. Although some of these patients may have had actual hepatic involvement (e.g., sarcoidosis), the majority of the Bromsulphalein elevations are probably due to fever, dehydration and congestive heart failure.

2. Again, the patients with multiple myeloma and nonmetastatic cancer have normal Bromsulphalein results far more often than those with other diseases.

3. There appears to be no correlation between the zones of albumin-globulin values and the Bromsulphalein test results.

4. Of the liver function tests examined, the Bromsulphalein test was most consistently abnormal in those patients with liver disease. Of 46 test results in liver disease patients, only two were normal. One of these patients had recurrent pancreatitis with questionable hepatic damage; the other had healed Laennec's cirrhosis (by liver biopsy). This confirms the generally held opinion that the Bromsulphalein is one of the most sensitive tests of liver function.

Serologic Tests for Syphilis

A serologic test for syphilis is ordinarily done on all patients admitted to this hospital, and is frequently done on patients seen in the outpatient department. Blood sera are tested by the qualitative VDRL method,[8,9] and positive reactions in the qualitative test are then examined both quantitatively [8,9] and by the Kolmer method.[10]

Of the 394 patients with hyperglobulinemia described in our previous paper,[1] serologic determinations had been done on 326. Of these, 296 were negative and 30 were positive. In the 30 patients with positive reactions, the charts were carefully examined for evidence of syphilis. In a number of cases such evidence was found, but in others the diagnosis was doubtful, with the possibility that a false-positive reaction had occurred.

Since this was a retrospective survey, made from clinical charts and laboratory data long after most patients had left the hospital, many of the cases had not had the serologic tests repeated or verified. Moreover, the treponema immobilization test [11] was not available for general use, so that the crucial information it provides in distinguishing true- from false-positive reactors was not obtained.

Within these limitations, each case was evaluated for the clinical and laboratory data which might support or refute a diagnosis of syphilis.

Patients were considered to be false-positive reactors if, in the absence of clinical evidence for syphilis, there was: (a) a negative serology within five years prior to onset of the present illness; or, (b) a VDRL which was positive in low titer and which reverted to normal without therapy; or (c) a negative or anticomplementary Kolmer reaction with borderline VDRL titer elevation; or (d) a disease known to produce false-positive serology,

e.g., systemic lupus erythematosus. With these criteria, the cases could then be aligned into positive, probable positive, probable false-positive and false-positive categories. Thus 13 of the 30 patients with positive VDRL results had unequivocal evidence of lues, and another four had good evidence for the disease. Seven and six patients, respectively, were considered false-positive or probable false-positive reactors. These 13 patients had a variety of diseases, and there appeared to be no correlation between the height of the globulin and the occurrence of the false reaction.

In our entire series there were 82 patients with hyperproteinemia, of whom 74 had had VDRL tests, and only four of these were positive. Two of these patients had unequivocal evidence of syphilis, and two were probably false-positive reactors, an incidence of 2.7% for false-positive results. This figure is much lower than the 23% incidence reported by Cardon and Atlas [12] in 34 cases of hyperproteinemia, although it remains higher than the normal occurrence rate they and others [13] have reported (one biologic false-positive per 4,000 persons).

Bone Marrow Plasmacytosis

Bone marrow examination was performed in 71 of the 394 patients with hyperglobulinemia. Some of these aspirations were done because the clinical diagnosis was obscure, others because the elevated globulin had led the physicians on the ward to suspect multiple myeloma or other diseases. A few were done for bacteriologic culture, and others to confirm hematologic diagnoses.

It is not the purpose of this paper to assess the diagnostic value of bone marrow examination. We were interested merely in confirming the correlation between hyperglobulinemia and bone marrow plasmacytosis, as observed by others.[14, 15, 16]

In this respect our data show that 44 of the 71 patients showed no increase in the plasma cells of the bone marrow. Twelve other patients had multiple myeloma, and in the remaining 15 patients without myelomatous disease the marrow showed a mild to moderate increase in plasmacytes. The diagnoses in the latter group of patients were: collagen disease, four; Laennec's cirrhosis, four; tuberculosis, two; chronic renal disease, two; syphilis with pneumonia, one; nutritional anemia, one; exfoliative dermatitis, one.

Discussion

Since the cephalin-cholesterol and thymol tests were first introduced, various investigators have attempted to explain the mechanisms involved.[17-21] It has been shown that both tests can be made positive (i.e., abnormal) by elevations in serum gamma globulin and by decreases in serum albumin.[18-21] A point of distinction between the two procedures is that serum lipids seem to play a more important role in the thymol reaction than they do in the

cephalin test.[18-20] Therefore, a high incidence of positive results for *both* tests would be expected in patients with hypergammaglobulinemia and/or hypoalbuminemia, and abnormal thymol results would be especially likely in patients with lipid disorders. (For example, the highest thymol turbidity values in the present series were found in patients with biliary cirrhosis who had very high serum lipid values.) Both of these flocculation-turbidity reactions, however, are affected by other factors which are still poorly understood and which may cause unpredictable variations in the results.[22]

In the present study the patients without overt hepatic diseases were differentiated from those with known liver damage in order to analyze the liver function tests in situations where a diseased hepatic parenchyma would presumably not be present, and where the abnormal albumin and globulin values would thus be major factors influencing the reactions. The degree of gamma globulin elevation was not determined in the patients reported here, since only the total globulin concentration was measured, and electrophoretic fractionation data were not available in sufficient quantities to aid in the present analysis. However, the average patient with hyperglobulinemia might be expected to have some elevation of gamma globulin, since a rise in the latter is the most common cause of hyperglobulinemia, although elevations of any or all of the globulin fractions can occur in individual cases.

Theoretically, therefore, we should expect certain cephalin and thymol abnormalities in this group of patients on the basis of elevated serum globulin or depressed albumin. This should be particularly true in diseases which cause a marked rise in gamma globulin by means of immune or antibody responses (such as inflammations or collagen disease), or in sarcoidosis, the pathogenesis of which is still obscure. On the other hand, these tests are more likely to be normal in multiple myeloma, nonmetastatic cancer or the "unclassified" cases, where total globulin elevations are not usually due to sharp rises in gamma globulin.*

The clinical data of this series, in general, support the above theoretic concepts. In patients without liver disease, the cephalin tests were more abnormal in the areas of lower serum albumin (Zones II and IV), and the thymol tests showed a greater incidence of abnormality in the high globulin areas (Zones III and IV). However, the cephalin tests did not appear to reflect globulin elevations so distinctly, nor did thymol test results seem greatly sensitive to changes in albumin values. Thus these clinical data suggest that the thymol reaction is, in general, more influenced by globulin elevation than is the cephalin-cholesterol flocculation test, which seems more dependent upon a lowered serum albumin. The patients with multiple myeloma, nonmetastatic cancer and "unclassified" diseases, as expected, regularly showed normal cephalin test results more often than did those with sarcoido-

* Very high values for serum gamma globulin are sometimes found in multiple myeloma, but these proteins do not physiologically behave as gamma globulin, although their electrophoretic migration places them in the gamma component.[7]

sis, collagen disease and inflammatory disease. This same situation held for the thymol test results, except that in inflammatory diseases this latter reaction was more apt to be normal. Possibly this is due to the fact that some patients with inflammatory diseases were debilitated, with subsequent depletion of serum lipids. Finally, it should be observed that, in patients without liver disease, the thymol test consistently was normal more frequently than was the cephalin reaction, and that in total, 63.1% of the thymol tests in this group were normal, as compared with 45.6% of the cephalin tests. This implies a decreased specificity for the latter determination as a "liver function test," but perhaps greater specificity as an indicator of abnormal serum protein relationships. Only in the sarcoid-collagen disease group did these two tests show similar results. The data presented here thus augment and expand the results of comparisons in these tests made by others.[28-29]

Our discussion thus far has dealt with the significance of the abnormal findings in these two tests. It should be pointed out, however, that in the absence of overt liver disease two thirds of the patients had normal thymol tests and almost one-half had normal cephalin tests, despite the marked distortion of the albumin-globulin pattern. Hyperglobulinemia, per se, should therefore not be considered as a cause of abnormality in these tests.

The serology data show that 13 of the 326 hyperglobulinemia patients tested gave false-positive serology reactions. The occurrence of this spurious result, frequently in conjunction with hyperglobulinemia, has been amply described in the literature,[12, 30, 31] and false-positive reactions are commonly observed in such diseases as pneumococcal and atypical pneumonia, infectious mononucleosis, infectious hepatitis, tuberculosis, malaria, lupus erythematosus, lymphogranuloma venereum, and a number of others. Complete listings have been given by Moore and Mohr.[32] The exact components of sera responsible for anticomplementary and false-positive reactions are not yet completely identified. Olhagen [33] found abnormal gamma globulin or an abnormal mid-beta globulin in nine sera with strong anticomplementary reactions, but in 48 sera which gave weak anticomplementary reactions he found a relative and absolute increase in gamma globulin which could not be distinguished from normal gamma globulin. On the other hand, Cooper et al.[34] could detect no electrophoretic difference between normal sera and certain sera which had given biologic false-positive reactions.

The relationship between bone marrow plasmacytosis and hyperglobulinemia has already been cited.[14-16] In our series of 71 bone marrow aspirations, 15 (21.1%) had so-called "benign" plasmacytosis. This is similar to the incidence reported in comparable studies by Berlin et al.[14] It is noteworthy that Clark and Muirhead [15] and Klein and Block,[16] who studied the diagnoses associated with a series of cases having bone marrow plasmacytosis, found many patients with "unclassified" diseases, analogous to the group found in the present study of hyperglobulinemia.[1]

Summary

1. An analysis has been made of the available results of liver function tests, serologic tests for syphilis and bone marrow examinations in a series of 394 patients with hyperglobulinemia.

2. In patients who did *not* have overt liver disease, cephalin-cholesterol flocculation tests were more apt to be abnormal in the presence of hypoalbuminemia, while thymol reactions appeared more sensitive to elevations in serum globulin. In this group of patients the thymol test was normal more frequently than was the cephalin test, although both reactions had the same incidence of abnormality in patients *with* liver disease.

3. In diseases where hyperglobulinemia is associated with a marked increase in gamma globulin, abnormal cephalin and thymol tests are found more often than in those diseases where the globulin elevation is more diffuse or restricted to other fractions.

4. The alkaline phosphatase and Bromsulphalein retention tests did not seem to correlate with abnormal albumin-globulin values, although the Bromsulphalein test was frequently abnormal in many patients without liver disease.

5. False-positive serologic tests for syphilis were observed in 4% of the patients, and did not correlate with either the diagnosis or the height of the serum globulin.

6. "Benign" plasmacytosis was found in 15 of 71 patients in whom bone marrow examination was performed. This examination also helped to establish or to confirm the diagnosis in 12 cases of multiple myeloma.

7. These data are compared with others in the literature.

Summario in Interlingua

Tests de function hepatic, tests serologic pro syphilis, e examines de medulla ossee esseva executate pro certes ex un gruppo de 394 patientes con nivellos de globulina seral de 3,9 g pro cento o plus. (Le nivello de 3,9 g pro cento es le limite superior del region normal secundo le methodo de Cohn e Wolfson.)

Pro le analyse del studios de function hepatic, le patientes esseva gruppate in duo categorias: Le prime categoria includeva le patientes qui habeva cirrhosis, malignitate hepatic, o altere morbos del systema pancreatico-biliari; le secunde includeva patientes con morbos que non es considerate como primarimente hepatic. Anormalitates del studios de function hepatic in le secunde categoria esseva del plus grande interesse, proque illos es communmente correlationate con disturbationes del stato del proteinas seral. Inter le patientes sin aperte morbo hepatic, 87 ex 160 tests de flocculation a cephalina-cholesterol esseva anormal. Le majoritate del resultatos anormal esseva constatate in patientes qui habeva hypoalbuminemia in ultra del anormalitates globulinic. Per contrasto, le tests de turbiditate e flocculation a thymol esseva anormal in solmente 59 ex 160 casos, e il habeva nulle correlation inter reducite nivellos de albumina seral e anormalitates del tests a thymol. Tamen, il pareva haber un certe correlation inter le numero de anormal examines a thymol e le grado de hyperglobulinemia. Le phosphatases alcalin esseva quasi completemente normal. Lor valores non pareva correlationar se con le nivellos de albumina o

globulina, ben que un numero de disturbationes del retention de Bromsulphaleina esseva observate. Non esseva un surprisa que multo plus frequente anormalitates resultava inter patientes con clinic formas de morbo hepatic ab le determinationes de flocculation a cephalina, turbididate e flocculation a thymol, phosphatase alcalin, e retention de Bromsulphaleina. Tamen, il non habeva un correlation inter le grados de anormalitate in le fractiones proteinic e le tests de function hepatic.

Pseudo-positive tests serologic pro syphilis esseva observate in 4 pro cento del patientes. Apparentemente illos non esseva relationate al diagnose o al nivello de globulina in le sero. "Plasmacytosis benigne" esseva presente in 15 e multiple myeloma in 12 ex 71 patientes pro qui aspirationes de medulla ossee esseva executate.

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COMMENTS AND OBSERVATIONS ON THE NATURE OF NARCOLEPSY *

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The interest in and the effort toward a better understanding of the nature of narcolepsy which made this paper possible were stimulated by a neuropsychiatric staff conference, the case presentation from which is given below in a somewhat condensed form.

Case Report

A 20 year old enlisted man in the United States Navy apparently began to have symptoms about seven years ago, when he noted the onset of a chronic feeling of lethargy and easy fatigue. In addition, he became aware of episodes of sleepiness which he described as follows: He feels his head growing heavy, his eyes beginning to close, and his body becoming weak all over. If he is standing his legs may buckle and, if sitting, he may not be able to support the upper part of his body. He then enters a semiconscious state which is not sleep, and during which he has some awareness of his surroundings and of the events taking place. At times he can remember conversations taking place during an episode. Following this, he may or may not go to sleep. These episodes may occur at any time of day, and there are no apparent precipitating factors. Their rate of occurrence varies from several times a day to once in a week or more. There has never been any tongue biting, incontinence or other convulsive components. In addition to his generalized lethargy and "spells" of sleepiness, the patient has noted that strong laughter may precipitate another type of episode. When the patient is moved to hearty laughter, he may suddenly "lose control" of his legs so that they begin to buckle; however, he has always been able to catch himself before falling to the ground. This sudden weakness of his legs is associated with similar weakness of his trunk, arms and neck, but is not associated with a disturbance in consciousness. This type of episode is of a momentary nature and is not followed by sleep. The patient gives no history of ever having experienced a severe head injury, and there is no evidence that he ever had encephalitis. The patient denies a present or past history of somnambulism or hallucinatory experiences. He also denies nocturnal sleep disturbance. The past history, gathered from direct questioning of the patient and from a letter from his mother, revealed that the patient's father was an alcoholic who mistreated both the patient and his mother. The mother and father were divorced when the patient was five years old. When he was seven his mother remarried. The patient's relationship with this man was adversely affected by the fact that his step-father refused to adopt him and give the patient his name. In his early grammar school years it was noted that the patient did not seem to keep his mind on his work, although he apparently had the ability

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to do so. Despite this, his grades were good. At the age of 10 or 11 it was noted that he seemed to require more sleep than usual. At the age of 12 or 13 the patient was given "hormone shots" to speed the development of his genitalia, which his mother felt were "too small." After six months of treatment development was normal. At the age of 13 the patient began helping in his parents' dry cleaning shop. He was rather antisocial and quiet, made friends infrequently, and did not evidence any interest in girls. It was at that time that the sleeping episodes began. His mother's description of one of those episodes follows: "He would be in a very relaxed state, head drooping, eyes rolled back (several times to such an extent I became frightened) and half open, mouth open and tongue hanging out, hunched forward. I would shake him and he would at times respond immediately or at times it took a while to wake him." At that time, the patient was discussed and seen with regard to his sleepiness by physicians, a psychologist and his teachers, but no conclusion was reached. At the age of 16 the patient had a minor accident, in which he ran into a car with his motor scooter. He apparently was amnesic for three hours, but there were no residual symptoms. His mother said: "This accident was not the result of a sleeping spell." It was at about this time that the patient began experiencing his cataplectic reaction to humorous stimuli. Again his mother's description of such a spell follows: "Tell L. a funny joke and see his reaction. He collapses completely, eyes rolled up, mouth drops, tongue hangs out and it seems his muscles give way altogether. I've seen him hold on to things to keep upright when laughing. At times it is uncanny to watch him in this state." The patient apparently enlisted in the Navy with the hope that his episodes would disappear in a new situation.

Past history and family history were otherwise negative, except that a third cousin has epilepsy. Review of systems was noncontributory.

On physical examination the blood pressure was 120/80 mm. of Hg, the pulse 80 and regular. The patient was a well developed, well nourished, somewhat obese young man. There were no abnormalities on general physical examination. Neurologic examination revealed a coöperative, well oriented young man who seemed somewhat dull and slow speaking. Cerebellar tests and examination of the cranial nerves were normal. The motor and sensory systems were intact. Deep tendon reflexes were equal and active, and there were no obtainable pathologic reflexes. There were no signs of meningeal irritation. Routine laboratory studies, including a complete blood count, urinalysis, blood serology and chest x-ray, were normal. X-rays of the skull were normal, and the pineal was visualized and normally situated. Spinal fluid examination was normal as to manometrics, sugar and protein content, cellular constituents and serology. An electroencephalogram revealed low amplitude fast activity, with a fundamental frequency of about 12 to 14 per second. There were no slow waves, and the tracing was considered to be within normal limits.

Just a day or two prior to the staff conference the patient was examined by a visiting neurologic consultant, who was of the opinion that he had an idiopathic narcolepsy syndrome. In the discussion, after the patient had been presented, the prevailing general opinion was in accord with that diagnosis.

The attempt to comprehend the narcolepsy syndrome has an interesting background history. Gélineau first used the term narcolepsy (meaning, sleep seizure[1]) in 1880.[2] Caffé also reported a patient with irresistible attacks of sleeping during that same year.[3] It is evident that abnormal diurnal sleep was of clinical interest much earlier. Willis described a case of morbid sleeping as early as 1677, and Fournier reported on a patient with

pernicious sleeping in 1817.[3] Westphal and Fischer reported similar clinical observations in 1877 and 1878, respectively.[4] Abnormal somnolence and lethargy were reported as early as the writings of Galen.[5] In 1841 Thuman and Friche described a patient who had episodes of loss of muscle tone without loss of consciousness.[8] Lowenfeld observed episodes of irresistible sleep and of loss of muscle tone in some of his patients. He concluded in 1902 that the latter symptom should be considered a part of a syndrome along with narcolepsy.[6] Adie first used the term cataplexy (meaning, to strike down [1]) in 1926.[7] In 1876 Mitchell described a symptom which he called night palsy and nocturnal paralysis.[8] This symptom was later more fully described by Pfister in 1903, by Rosenthal in 1927 and 1928, and by Lehrmitte in 1927 and 1928.[9] It came to be called sleep paralysis, and is also now included in the narcolepsy syndrome.[10, 11, 9, 4, 12, 13, 14, 15, 16] As the syndrome became more frequent and was of increased clinical interest, it became apparent that transient hallucinative and hypnogogic episodes, directly related to or independent of the other symptoms, were also to be considered in the narcolepsy syndrome.[4, 17] Brain also includes somnambulism in the syndrome.[13]

In his original discussion of narcolepsy, Gélineau insisted that it be considered a disease unto itself.[2] It may be possible that his dictum greatly impeded the understanding of the nature of narcolepsy, and much effort has gone into attempting to maintain Gélineau's original premise. As it became apparent that the symptoms of narcolepsy could in some cases be etiologically related to such primary illnesses as encephalitis, trauma to the head, syphilis, brain tumor, diabetes mellitus, pituitary disorders, cerebral arteriosclerosis, influenza, hyperinsulinism, epilepsy, multiple sclerosis and polycythemia vera, a classification of narcolepsy came into being and those patients were considered to have symptomatic or secondary narcolepsy.[3] Patients who evidenced no culpable primary disease were and are considered to have genuine narcolepsy or hypnolepsy (true narcolepsy, Gélineau's disease, idiopathic narcolepsy, cryptogenic narcolepsy).[6, 17, 7] Jelliffe and Wilson were among the first to insist that narcolepsy should not be considered a disease per se or a modus sui generis. They suggested that narcolepsy be considered as a syndrome which might be seen, in its entirety or in part, in a variety of conditions, including psychiatric disorders.[5, 14] This latter concept has been slow to gain acceptance.[18, 19, 4] It would seem that idiopathic or cryptogenic are less distasteful descriptive terms than is psychogenic, even though they may be much less illuminating.

The complete narcolepsy syndrome consists of narcolepsy, cataplexy, sleep paralysis, hallucinative states and somnambulism.[12] Gélineau described narcolepsy as "characterized by an imperious desire to sleep, sudden and of short duration, reproducing itself at intervals more or less closely related." [2] These diurnal naps may come on at any time, even in the midst of enjoyable activity. Monotony tends to bring them on and diversion tends to counter-

act them. The patient can usually be easily aroused. The episode may last from a few minutes to several hours. The patient may be aware of an impending episode and may be able to fight it off, but the effort of doing so may precipitate an episode of cataplexy. On occasion, the patient may be somewhat aware of his surroundings. In a typical episode of narcolepsy the electroencephalogram exhibits those changes seen in normal sleep. Cataplexy is an episode during which consciousness is preserved, even though the patient suddenly loses all power of movement and posture. He sinks into a helpless mass of toneless muscle, usually with the eyes closed. These episodes are usually precipitated by strong emotion and characteristically last only a few moments, although they may last until the precipitating emotion is controlled. This symptom is usually found in conjunction with narcolepsy and is seldom seen in patients who do not also have narcolepsy. Sleep paralysis closely resembles cataplexy in that control of the motor function is lost. However, instead of coming on in response to an emotional stimulus, it occurs as the patient goes to sleep or awakens. The patient is conscious but is unable to move a single muscle. A touch, or the ability to move slightly, usually terminates the episode. Some individuals suffering from the narcolepsy syndrome also experience transient but vivid hallucinative states, which are usually visual rather than auditory. These hallucinations may be quite terrifying, and may take place while the patient is awake or while awakening or going to sleep. Somnambulism, which might be considered the reciprocal of cataplexy, is also seen in some patients with the narcolepsy syndrome. The symptoms which compose the syndrome may occur in wide variation and combination, narcolepsy itself usually being the most frequent and consistent symptom.[4, 6, 9, 16, 20, 13, 10, 15, 4, 21, 11, 22, 23]

The symptoms of the narcolepsy syndrome most often begin between puberty and early adult life. Daniels, in his review of 377 patients, found that the onset was before the age of 21 in 52%, and before the age of 26 in 70%. The illness was found twice as often in men as in women. He also noted a tendency to gain weight after the onset of the symptoms, and a decrease in libido was noted in 10 to 15%. In some of the patients studied the symptoms had been present for as long as 40 years without evidence of untoward effect on the general health. Fluctuation in the severity and frequency of the symptoms was noted to have taken place in patients whose illness had been present and untreated over some period of time.[4]

It would appear that the incidence of the narcolepsy syndrome has increased significantly since World War I. Prior to that time the reporting of a case was relatively rare.[24, 6, 25, 4] This rarity might in part be explained by lack of awareness of the syndrome and failure to make the diagnosis. This would, however, be an inadequate explanation when we consider that Wilson reported in 1928 that he had actively looked for a patient with narcolepsy for a period of 20 years before he was successful in his search.[14] No doubt some of the sudden increase in incidence after World War I is an

expression of narcolepsy secondary to the numerous cases of epidemic encephalitis in 1918. Wilson and Daniels were unable to explain the increased incidence satisfactorily, but they were reluctant to believe that the entire increase was made up of patients with chronic encephalitis.[4, 14] That reluctance is supported by a review of the literature up to 1931 which was made by Notkin and Jelliffe. Out of 179 cases reported, only 29, or 16.2%, were patients with a postencephalitic syndrome.[6] Levin has proposed a very interesting explanation for the increased incidence, from an entirely different viewpoint, based on his belief that the symptoms of the narcolepsy syndrome are an expression of conditioned inhibition of the brain. He believes that, as life has become more complex, man has acquired more defense reflexes and a corresponding increase in the amount of cortical inhibition. The narcolepsy syndrome becomes manifest in those individuals who are not able to compensate for the increased inhibition.[24] This concept of narcolepsy will be touched on again later.

Shortly after narcolepsy became a subject in medical literature, patients being considered for that diagnosis were subjected to a classification consisting of three categories: patients with idiopathic narcolepsy; patients with symptomatic narcolepsy (symptomatic of or secondary to physical disease); patients with some symptoms resembling narcolepsy but who were considered to be suffering from hysteria, petit mal or some other previously noted disease and who should not be classified with the narcolepsies.[6, 17] In effect, then, actual narcolepsy is confined to two categories: idiopathic narcolepsy (etiology unknown), and symptomatic narcolepsy (symptomatic of or secondary to physical disease). Such a classification would seem to the present authors to be unnecessarily rigid and, perhaps, in some instances detrimental to an optimal understanding of the patient's illness.

The large body of neurologic literature dealing with the etiology of the narcolepsy syndrome embraces two predominant (and somewhat opposed) theoretic concepts: (a) that of Levin, utilizing Pavlov's concepts of inhibition, disinhibition, etc.; and (b) those concerned with focal discharge from diencephalic and mesencephalic centers and from their connections with the cerebral cortex. Considerable theoretic confusion and conflict emanate from the various writings on this subject. This is readily understandable in view of our lack of knowledge concerning the process of sleep itself. Notkin and Jelliffe briefly reviewed some of the multitudinous and divergent explanations of this process presented over the past 110 or so years: (a) cerebral hyperemia (Shepard); (b) cerebral anemia; (c) interruption of the conductivity of nerve centers, isolating the hemispheres from the outside world (Purkinje); (d) reflex inhibition; (e) cerebral inhibition (Pavlov); (f) chemical theories (Pieron's "hypnotoxin," excess of lactic acid, etc.); (g) an instinctive biologic process of defense to render an animal immune to previous exhaustion; (h) return to an intra-uterine life (psychoanalytic); (i) physiologic sleep center in the posterior wall of the third ventricle.[6]

Recognition of this unorganized state of our knowledge concerning sleep is a necessary prerequisite to evaluation of and inquiry into the etiology of narcolepsy.

Levin freely utilized the concepts of Pavlov in his theoretic explanation for the pathogenesis of narcolepsy.[9] Sleep consists in widespread inhibition of the cortex, protecting it from undue fatigue. In the alert animal this inhibition exists only in scattered areas of the brain, whereas widespread irradiation of inhibition causes the animal to sleep. The patient with manifest symptoms of narcolepsy possesses a brain unduly susceptible to these inhibitory influences. Moreover, he possesses a brain in which "localized inhibition" or "localized sleep" readily occurs. Thus, narcolepsy itself is the result of inhibition of both the "substrate of consciousness" and the "motor and tone centers." Cataplexy, however, involves inhibition or localized sleep of the motor and tone centers only. In sleep paralysis, inhibition of motor and tone centers occurs before or after inhibition of the substrate of consciousness: before, when the sleep paralysis is attendant upon going to sleep (predormitial paralysis), and after, when the sleep paralysis occurs upon awakening (postdormitial paralysis). The restless nocturnal sleep and somnambulism sometimes seen in narcoleptics represent localized sleep affecting the substrate of consciousness but not the motor centers. Finally, hypnogogic hallucinations are the result of "imperfect" inhibition of the substrate of consciousness, during which the patient is awake but consciousness is defective. "Disinhibition," the dispersion of inhibition by an excitatory process, explains the ready recovery from an attack of cataplexy and sleep paralysis induced by a mere touch. Levin develops his theory further by suggesting that in those predisposed, voluntary inhibition of a powerful reflex (such as that to pain) can induce a narcoleptic episode; thus, the occurrence of an attack in a dentist's chair, in a soldier on sentry duty (inhibition of the reflex to sound an alarm when the approaching figure is found, at the last moment, to be an ally), under bombardment (suppression of the tendency to run).[28]

The second view, that dealing with a focal sleep mechanism in the region of the hypothalamus, and involving cortico-hypothalamic connections, boasts somewhat stronger support. Experimental, clinical and pathologic studies give credence to this concept. O'Connor is of the opinion that interruption of cortical fibers results in disorganization of the sleep cycle, whereas damage in the vicinity of the hypothalamus causes somnolence.[27] Earlier, Gill and others described the "third ventricle syndrome."[28] It was noted that organic disease involving this region, whether it be the result of encephalitis, trauma, tumor, etc., might produce one or more of the following: disturbance of the sleep cycle (narcolepsy, hypersomnia, etc.), disturbance of temperature regulation, disorder of water balance, abnormal appetite (bulimia), abnormalities of fat storage, and disorders of the reproductive system (menstrual irregularities, decreased libido, change in secondary sex

characteristics, etc.). These constitute a series of vegetative symptoms resulting from organic affection of hypothalamic nuclei. Gill described personally observed case histories in which head injury caused narcolepsy, cataplexy and several of the other third ventricle symptoms mentioned above.[19] Thus, so-called secondary or symptomatic narcolepsy would appear to have a sound basis in disorder of the hypothalamus; specifically, of those hypothalamic nuclei concerned in the regulation of sleep. It has long been recognized that patients suffering from "idiopathic" narcolepsy frequently exhibit obesity, menstrual irregularities, decreased libido, polydipsia and other symptoms of the "third ventricle syndrome." It would appear logical to assume that idiopathic narcolepsy represents a true "functional" disorder of cortico-hypothalamic "sleep-cycle" impulses. One might call upon the (oft called upon) possibly analogous situation of idiopathic epilepsy where, presumably, we are dealing with a "functional" disorder of other diencephalic centers. The authors, however, would tend to disagree with Gill that idiopathic narcolepsy is a manifestation of inapparent infection by an attenuated strain of the virus of encephalitis lethargica. Obvious cases of this disease only rarely develop the narcolepsy syndrome.

To return to symptomatic narcolepsy, Ethelberg recalls that cataplectic attacks may occur not only in disease of diencephalic and mesencephalic centers but also in cases of tumor.[29] It is believed that these episodes are manifestations of tentorial herniation of the midbrain, with consequent compression, resulting from increased intracranial pressure. It is rare for cortical lesions to induce narcoleptic or cataplectic attacks (the latter much more frequent than the former). This has been observed, however, with neoplastic involvement of the mesial and anterior surfaces of the frontal lobes. Ethelberg reported two cases in which a depressed skull fracture caused a 2 cm. circular depression on the left and right frontal cortex, respectively. Both patients exhibited cataplectic episodes which ceased after craniotomy and elevation of bone fragments. Experimentally, relatively mild stimulation of certain areas ("suppressor bands") in the motor cortex of animals induces relaxation of muscle tone. However, stronger stimulation is frequently accompanied by focal or generalized epileptic seizures. Ethelberg suggests that organic lesions (tumor, depression by fracture) of the motor cortex induce partial arterial obstruction, ischemia, and consequent abnormal electrical discharge. If "weak," the impulse is conveyed to subcortical levels and limpness ensues. If "strong," contiguous areas of the cortex discharge, with a resultant focal or generalized seizure. The similarity between the cataplectic episodes following focal cortical lesions to those of the idiopathic narcolepsy syndrome supports a cortical-hypothalamic concept of sleep and its aberrations. It is likely that the function of sleep, in common with other functions, has become progressively corticalized in the course of philogenetic development.[20] Davison and Demuth, in their series, also found that sleep disturbance could result from

either cortical or diencephalic lesions.[31] W. J. Nauta, performing destructive lesions in rats, defined a "waking" center in the mammillary bodies (caudal hypothalamic region), and a "sleep" center in the suprachiasmatic (preoptic) region. He also concluded that the sleep center did not act directly on the cortex but by inhibition of the waking center. This matter, however, is unsettled. Palmer relates that in the course of development of the prosencephalon, and as integrative control has passed from caudal to rostral centers, two systems have defined themselves: the diencephalic system, which functions during sleep, and a telencephalic system, involving the cortex, whose functional relationship with the diencephalon is disrupted during sleep.[30] Defective relationship between these two systems during the waking state, it is inferred, may result in a variety of conditions: narcolepsy, the Klein-Levin syndrome, petit mal, akinetic epilepsy, etc. Moreover, it is suggested that some aspects of mental disorders may also be the result of faulty integration between the two systems. If this hypothesis is correct, it is possible that the whole structure of psychoanalysis, and especially the recent psychopharmacologic technics, operate on the "primitive (diencephalic) mind," or enhance diencephalic-telencephalic integration.

Dynes and Finley obtained electroencephalographic tracings in 22 cases of narcolepsy.[32] Seventeen of the 22 patients had normal wake records. Sixteen of these 17 had narcoleptic attacks during the recording, and the patterns developed during these attacks were in all cases similar to those observed during physiologic sleep. The five remaining patients exhibited atypical or abnormal wake records, and none of them experienced a narcoleptic attack during the recording. The abnormalities observed did not resemble the electroencephalographic patterns of normal sleep. In three of these five tracings, atypical rapid activity of no probable clinical significance was seen. The remaining two exhibited random slow activity consistent with organic disease. In all five patients abnormal neurologic signs could be elicited, and narcolepsy without cataplexy was observed. The sleep activity seen in the tracings of the 16 patients with normal electroencephalograms did not resemble epileptic patterns, and none of the patterns could be induced by hyperventilation. The K complex, seen in normal sleep as the result of sound stimuli, was also observed in narcoleptic sleep. Cataplexy could not be induced during electroencephalographic recording in this series. Other authors have occasionally observed electroencephalographic abnormalities, but rarely if ever have they been of a paroxysmal nature.

The narcolepsy-epilepsy controversy alluded to above persists. Many tend to see a relationship between narcolepsy and epilepsy. Wilson stressed "periodicity, recurrence, abrupt onset, interference with the stream of consciousness, brevity, often quick return to normal." Palmer believes akinetic epilepsy, petit mal and narcolepsy are related diencephalic disorders.[30] He recorded the history of a patient with a typical narcolepsy syndrome, with all its components, the electroencephalogram of whom "yielded the impres-

sion of dysrhythmia." Symonds described epileptics who, later in life, developed unmistakable manifestations of the narcolepsy syndrome.[33] He also compares "reflex" epilepsy and cataplexy, noting that in both disorders certain common stimuli may incite a seizure: noise, startle, sexual orgasm, laughter. On the other side of the fence, Adie stressed the unusual association of narcolepsy and epilepsy in the same patient.[7] Dynes and Finley point out the dissimilar therapeutic approaches to the two disorders.[32] Whereas epilepsy responds to depressants such as barbiturates and bromides, narcolepsy must be treated with stimulants such as Dexedrine, Benzedrine, ephedrine, desoxyephedrine, etc.[34, 35, 36, 37] Indeed, claim has been made of success in the temporary arrest of narcoleptic episodes by the use of stellate ganglion block.[28] Again, if the disorders are truly expressions of a single basic neurophysiologic disturbance, would it not be expected that narcoleptics exhibit the spike-wave complex of idiopathic epilepsy, or at least some consistent, unequivocal electroencephalographic abnormality? Why is a hereditary trait, so typical of idiopathic epilepsy, absent in idiopathic narcolepsy? Few authors conceive of epilepsy as psychogenically determined, yet recent trends appear to incriminate basic personality disturbances as potent factors in the etiology of narcolepsy. Until these questions are answered the present authors would tend to agree with those who hold that idiopathic narcolepsy and idiopathic epilepsy spring from dissimilar neurophysiologic disturbances.

Intensive studies of narcolepsy have failed to demonstrate it to be a disease entity per se, and the studies of a large percentage of patients with the narcolepsy syndrome have failed to demonstrate a current or past physical illness of which the narcolepsy symptoms could be considered in any way symptomatic. Even so, there has been strong reluctance to a consideration that a psychiatric approach might be able to remove at least some of the lack of understanding inherent in a well defended idiopathic impasse.[4, 19, 17, 38] This reluctance may be in some way related to the traditional manner of thinking about unexplained narcolepsy which was dictated and handed down by Gélineau, and also to the psychologic block that may be implicit in thinking of a complex as being idiopathic in origin. Another factor may have been the discovery of fairly successful drug control of narcoleptic symptoms at the time the syndrome was being given considerable attention in medical literature.[34, 39, 4, 18, 17, 20, 35, 12, 3] Removal of distressing symptoms is, of course, not to be frowned upon or belittled; however, removal does not necessarily mean completeness of treatment. Even perfect control of symptoms by medication does not indicate a therapeutic triumph if there is any possibility of removing the cause of the symptoms. The necessity for a continuous medication crutch could be as destructive to a patient's concept of himself and his capacity for comfortable interpersonal relationships as the presence of distressing symptoms.

Given a typical patient with the narcolepsy syndrome without demon-

strable evidence of culpable physical illness, and without overt manifestations of neurosis or psychosis, there are several points which suggest consideration of psychogenicity. Narcolepsy usually appears at a stressful time in the emotional maturation of the individual. The symptoms could represent an unconscious self-punitive attempt at escape from those stresses, and could be perpetuated as a method of relating or avoiding relating, as the current stress suggested. The two-to-one incidence ratio of men over women could be related to those same stress factors in terms of the greater competitive expectations (external stress) placed on men by society, and the potential insecurity which may be inherent in the weakening of the family structure (internal stress) in recent years. This latter consideration could be related to the increased incidence of the narcolepsy syndrome since World War I, as suggested by Levin,[24] and also to the greater sophistication of neurotic symptoms and the decreased incidence of classic conversion hysteria since World War I. The short duration and the marked degree of disturbance of function of the individual in the face of abrupt and usually complete recovery from an attack do not necessarily suggest organic disease, nor does the number of years that the syndrome may be present without evidence of decrease in general health. The weight gain often seen soon after the onset of the syndrome could be interpreted as the expression of an additional emotional defense through increased oral activity. The great variation in frequency of attacks and in the presence and severity of the various symptoms composing the syndrome suggests psychogenicity, as does the occasional presence of hallucinative and hypnogogic experiences and somnambulism. The lack of a usual disturbance in the nocturnal sleep pattern accompanying the abnormal diurnal sleep pattern and the lack of abnormal electroencephalographic findings detract from the likelihood of an etiology based on physical pathology. The fact that the symptoms of the narcolepsy syndrome respond to medication which gives a relatively small stimulus to the higher centers of the brain questions the possibility of organic disease, or a persistent and physically determined disturbance in neurophysiologic function. This consideration might be added to if we remember that the medications which are utilized successfully in the symptomatic treatment of the narcolepsy syndrome are also quite often used with good success in certain patients experiencing a psychogenic depression of affect and mood. Another interesting potential aspect of the giving of medications to a patient with the narcolepsy syndrome might be mentioned in this connection. If one is interested only in the achievement of a symptom-free state in exchange for medication and regular visits with the patient, how can one be sure that the freedom from symptoms is not dependent on a resolution of etiologic conflicts which the patient might be able to make by virtue of experiencing a giving, accepting, approving, protective, encouraging, limited and structured relationship with a kind and understanding but firm parental substitute?

Levin has contributed several interesting papers on narcolepsy in the light of Pavlov's theory that sleep is widespread cortical inhibition.[9, 26, 24, 40-42] He understands the manifestations of the narcolepsy syndrome to be expressions of inhibition of impulses, thoughts or behavior the recognition or expression of which the individual could not tolerate in himself, or feels would not be acceptable by individuals whose acceptance and approval he must have to be comfortable. Thus, the symptom of the narcolepsy syndrome, particularly narcolepsy and cataplexy, can protect the individual from aggression and resultant guilt and at the same time be quite hostile. Levin is of the opinion that the increased complexity of modern living has made it necessary for modern man to acquire more defense reflexes and an increased amount of cortical inhibition. He believes that this increased inhibition is compensated for by most individuals, but that when the cortex is inhibited with undue ease, symptoms of the narcolepsy syndrome appear. Levin blames the increased complexity of modern life and the accompanying increase of acquired defense reflexes for the marked increase in the incidence of the narcolepsy syndrome since World War I. The above theories are of value to these authors in that they seem to be added proof that idiopathic narcolepsy might well be considered to be psychogenic, at least until appropriate psychiatric evaluation has been conducted.

Brain takes exception to the theories of Pavlov by pointing out that, even though sleep and inhibition may coincide, they need not be identical. He is of the opinion that idiopathic narcolepsy is simply the exaggeration of a natural tendency to drowsiness. He considers cataplexy to be a localized sleep affecting only the centers of the brain concerned with movement and posture, and sleep paralysis to be the expression of the failure of a uniform spread of sleep over the nervous system, the postural and motor centers having fallen asleep while the conscious levels have remained awake. He considers the hallucinative states to represent dissociated consciousness, and somnambulism to be the converse of cataplexy.[12]

The concepts of Brain bring us no closer to an understanding of why the symptoms of the narcolepsy syndrome appear in the absence of a primary disease process, except that his belief that narcolepsy is the exaggeration of a natural tendency to drowsiness raises an important point. This reminds us that almost everyone has taken an irresistible quick nap similar to narcolepsy at one time or another when faced with a boring situation, or in a situation where one might rather have expressed hostility or aggression. Most individuals have experienced a situation in which they were so overcome with laughter that they became weak all over, or were so angry or afraid or overcome with guilt that they could not control their muscles and had to sit for a time until control returned. Perhaps it is true that on occasion, as we go to sleep, the motor and postural aspects of our being may go to sleep while consciousness lolls in a hypnogogic state between awareness and sound sleep. Certainly we are all aware of transient hypnogogic hal-

lucinations or distortions and somnambulistic episodes in otherwise normal individuals. This recognition of elements of the narcolepsy syndrome, outside of reference to ill individuals, reminds us that in all the broad field of psychogenic illness the distortion and aberration are in terms of quantity. Again the question is raised as to whether idiopathic narcolepsy is idiopathic.

Wilson, Notkin and Jelliffe suggest that narcolepsy and cataplexy may be defense mechanisms, and compare them to the defense mechanism of certain animals who fall into immobility when frightened.[14, 6] Narcolepsy and cataplexy might then be thought of as relics of primitive reactions, rather than as the result of increased cortical inhibition, as suggested by Levin. Such a concept would be in agreement with Fenechel, who sees narcolepsy as the archaic pattern of all repression, a generalized repression with transient elimination of all consciousness.[43]

Murphy has reported seven patients with the narcolepsy syndrome, including examples of both the idiopathic and the symptomatic type. He concluded that narcolepsy is a borderline syndrome common to cases of both functional and organic brain disease, and that either damage to or inhibition of cortical tracts depresses cortical control and releases a polyphasic sleep rhythm, as is seen in young children and the lower animals, in place of the monophasic sleep rhythm usually observed in adult humans and other higher animals.[8]

Coodley successfully treated, psychotherapeutically, a patient who had experienced narcolepsy, cataplexy and hypnogogic episodes. He was of the opinion that the psychodynamics of the patient's illness were not unlike conversion hysteria. He also concluded that narcoleptic episodes, unlike cataplectic episodes, are not related to specific precipitating situations in each instance but are reactions to more pervasive conflicts.[44] Spiegel and Oberdorf agree that narcolepsy is very closely related to conversion symptoms. They report the successful psychotherapy of a 49 year old woman with narcolepsy. Although she was hospitalized and treated quite intensively, it was several months before it became apparent that her symptom was the means to unconscious gratification of forbidden wishes as well as protection from guilt and punishment for the wishes. It should be pointed out that no deep psychoanalytic interpretations were made during this patient's hospitalization, and that her improvement was dramatic after she became secure enough in her relationship with her therapist to be able to express herself in a cathartic confessional interview.[45]

Davison points out that sleep is a psychobiologic protection against mental and physical exhaustion which is accomplished by regression with a denial of reality and an apparent blocking of motor activities. He concludes that sleep can be and is utilized as an escape from conflict between an individual's instinctual drives and the restrictive world around him. He reported the psychoanalytic treatment of five patients with the narcolepsy syndrome.[46] Langworthy and Betz have likewise concluded that the nar-

colepsy syndrome may be a response to emotional conflicts. Their clinical studies led them to conclude that the basic conflict is in the area of strivings for autonomy and self determination.[47] Roth arrives at a similar opinion when he concludes that ambivalent feelings toward the mother are the psychodynamic core of the narcolepsy syndrome.[48] Missriegler has also concluded, from his successful psychoanalytic therapy of a patient with the narcolepsy syndrome, that the latter is basically a neurosis.[49]

Barker, in a report of his study and treatment of four patients with the narcolepsy syndrome, agrees with Langworthy and Betz when he concludes that the characteristic conflict seen in these patients is between the emotional need for relationships with others and the denial of that need expressed in a struggle for independence, the symptom being the solution to and the punishment for the emotional impasse if the content is consciously unacceptable and threatens to become conscious.[45] Barker also points out that, since episodes of narcolepsy are brief interruptions of the organism-environment relationship, and since the episode is behavior, some relationship must exist between it and the situation in which it occurs.[50]

The above findings and conclusions of investigators and therapists of the narcolepsy syndrome of other than symptomatic etiology are included as an additional effort to reinforce the position that perhaps idiopathic narcolepsy is not so idiopathic after all. We reach back over the years between for one more reinforcement and point out that Gélineau concluded that, by bolstering the morale of the patient by means of psychotherapeutic measures, he was able to effect greater improvement than by any other form of treatment available.[2]

When the case which we reported above was presented to the staff conference he had been taking 5 mg. of Dexedrine Sulfate three times a day for several days and was subjectively free from any symptom of the narcolepsy syndrome. His adjustment on the ward had been a rather passive one. Although he was alert and coöperative, he was slow in both mental and physical participation in ward activities. Perhaps his overt attitude could best be described as covertly hostile disinterest and indifference. There was no genuine relating with other patients, and there was no outward expression of anxiety and actual concern in regard to his longstanding symptoms and his having been hospitalized because of them. A question was raised as to whether additional psychiatric evaluation might shed some light on the etiology of his narcoleptic symptoms. Such a consideration had to be evaluated in the light of administrative as well as purely medical factors. Ultimate disposition of this man from the sick list was possible by either of the usual two clear-cut avenues available to any naval medical officer on hospital duty. Depending upon the circumstances, a patient could be discharged from the service or returned to duty. The former avenue of disposition did not seem open in that the expressed reason for his incapacity at duty and his hospitalization had already been removed. However, it also seemed probable that the mere removal of his symptoms had done little to make him significantly more fit for duty than he had been prior to his hospitalization, in that the medication could not be expected to remove the feelings, attitudes and defenses which had built up in relationship to the presence of the symptoms of the narcolepsy syndrome over a period of several years. In addition, if it was true that the manifestation of the narcolepsy syndrome was the outward expression of uncon-

scious emotional conflicts, then removal of the symptoms by medication could no more be expected to alter the basic problem than could aspirin be expected to resolve the emotional forces expressed by a tension headache. It was decided to retain the patient on the sick list in an attempt to help him to be more comfortable and more capable of the duties of his rate when he was returned to duty later. To this end, a program of medication control, clinical observation and evaluation, including neurologist, psychiatrist and clinical psychologist participation, was begun.

For a period of two weeks the patient was placed on a regime of 10 mg. of Dexedrine Sulfate and 64 mg. of amobarbital three times a day (early morning, noon, and late afternoon). This method of medication was selected to insure adequate stimulation of the higher cortical centers throughout the day without untoward side-effects. During this period of medication the patient experienced no manifestations of the narcolepsy syndrome, but other manifestations became apparent. He became more friendly, outgoing and sociable. He participated in ward activities and craft projects with increasing pleasure and enthusiasm. He was then placed on two weeks of placebo medication. During that two week period his increasing capacity to relate more comfortably continued. He had no definite symptoms of the narcolepsy syndrome; however, there was a tendency to feel worn out by the end of the day, and on at least one occasion he fell asleep while watching a movie in the evening.

On the last day of placebo medication the patient was given a battery of psychologic tests, including the Rorschach, Bender Gestalt, the Recall Bender and Figure Drawings.* The Rorschach responses evidenced a great deal of perseveration of thought, but without any of the usual signs of an organic or schizophrenic condition often seen in perseveration. He made, almost exclusively, whole responses without human figures or human movement, and the perseverated content material included, for the most part, home objects such as pots, door knockers, ornamental vases, lamps, drawer knobs and family crests. The perseveration and the content were considered to be the expression of strong repressions. There was evidence of prestige strivings, and a passive, receptive, feminine orientation, and a great deal of ambivalence and anticipation of rejection from the mother figure. The father figure was seen to be cold, distant and inaccessible. There were many obsessive-compulsive traits throughout the Rorschach material. The patient also exhibited a peculiar crescendo response to affective stimuli. The Bender Gestalt indicated a great deal of hostility, feelings of phallic inadequacy and masculine strivings. The Recall Bender was characterized, in the main, by constriction, feelings of isolation and affective isolation with a potential for depression. The Figure Drawing test also indicated identification difficulties, the female figure being hostile and masculinized, and the male passive. There was no evidence of body image distortion, but there was indication of a reaction-formation against the threat of extension of the body image into the environment.

Following the placebo medication the patient was taken off of all medication for four weeks, and early in that period he was given the Wechsler-Bellevue (Form I) Intelligence Test. He achieved a verbal score of 119, a performance score of 106 and a full score of 115. During the testing he seemed less inhibited and bored than on previous testing, and at times was slightly flip and somewhat condescending. His best single scoring was a perfect score on Digit Span. The poorest score was on Digit Symbol, indicating poor visual-motor coördination in a setting of new learning. The Goldstein Block Test was also administered. There was no evidence of impairment of capacity for ideational shift, but the test was performed in a highly compulsive manner.

During the first half of the month of no medication the patient continued to make a very good participating ward and hospital adjustment. He was made ward

* Acknowledgment is gratefully made to Mr. Robert S. McCully for the excellent psychologic testing which he did in connection with this study.

master-at-arms, a position of responsibility, which he occupied until his discharge from the hospital.

After two weeks of no medication and no symptoms except for late afternoon and evening fatigue and occasional falling asleep in the evening while watching television or a movie, direct psychiatric participation was included in the study. The patient had been observed for a period of six weeks: two weeks on medication; two weeks on placebo medication; two weeks without medication. In marked contrast to his pre-hospitalization status, he had experienced no episodes of cataplexy, nor had he experienced any classic diurnal naps. Psychologic testing had revealed average intelligence, in addition to many deep-seated neurotic conflicts, marked repression and constriction and rigidity of the capacity to relate. At that point a series of psychiatric interviews over a period of six weeks was planned: two interviews per week during the first two weeks, and one interview each week thereafter. It was considered necessary to place this time and schedule structure on the psychiatric participation in the beginning, even though it was recognized that the plan might have to be changed later. This was to be a controlled and structured doctor-patient relationship, a relationship in which the patient might explore his feelings about his illness and being hospitalized and a relationship in which he might find acceptance of, respect for, and understanding of his feelings as an attempt was being made to help him experience an emotional catharsis in regard to his current life situation and, to some extent, to some aspects of his past life experiences.[51] In order to approach such goals without establishing a necessarily ongoing treatment relationship, it was considered wise to have a time and schedule structure as a point of departure. With the exception of the preconceived length of this doctor-patient relationship, the technic of time and schedule structure utilized varies little from that in most face-to-face psychotherapeutic efforts which are oriented by (not toward) psychoanalytic concepts.

The patient came to this relationship well prepared to participate. He was alert, friendly and coöperative. He knew the psychiatrist through weekly rounds, and he knew from direct discussion with the neurologist that he was being seen by the psychiatrist because the latter was interested in helping him and was also interested in the possibility that his symptoms could in some way be related to feelings and attitudes that he had been unable to express in a direct manner. As often happens with a well prepared and well motivated patient, he afforded in his first interview an opportunity for observation and understanding of many pertinent emotional forces which were less obvious in later interviews. After some facilitating comments by the psychiatrist, the patient filled the entire hour with a catharsis of feelings and highly charged content material, leaving little necessity for verbal participation on the part of the psychiatrist except for an occasional directional comment. Possibly because of a preconceived idea of what was expected of him, the patient talked about himself in a longitudinal sequence. His memories of his cruel and alcoholic father were filled with hostility and bitterness. The divorce of his parents and the subsequent struggle of the mother to make a living for her son and herself left him very emotionally dependent upon his mother, with a very submissive attitude toward her and a driving need to make up to her for the sacrifices she had made for him. By the time the mother remarried, when the patient was seven years of age, she had established a successful garment cleaning business in the large southern city where they lived. The step-father had only recently immigrated to this country from Italy. He was made a partner in the cleaning business. Both the mother and step-father worked in the business. From the beginning, the patient has seen the step-father as a cold, menacing, money-grabbing competitor with whom no positive father-son type of relationship has been formed. The marriage also left him with a feeling of abandonment and betrayal on the part of his mother. When the patient was about 10 years old, a son was born to his mother and step-father. Two years later another

son was born. The patient over-reacted to those two events by taking over a great deal of the care and mothering of his step-brothers, as well as a large part of the housekeeping. This behavior, of course, was with the approval of his mother and was continued until he entered the Navy. Another very important sequence of events took place when he was about 10 years of age. Financial reverses, which he blamed on the step-father, caused a loss of the family business and necessitated the sale of their house and their large yard with beautiful trees. A smaller cleaning business was bought, in a much less desirable section of the city, and the family lived in an apartment over the place of business. His mother worked harder and put in longer hours than previously, and a large proportion of the care of the home and the step-brothers was placed on the patient. He found adjustment to a new school, new friends and a new community very frustrating and uncomfortable, and he became a rather passive participant in all three areas. It was at this time that he began to have occasional, irresistible diurnal naps. It was not until two or three years later, when his cataplectic episodes appeared, that his mother gradually became aware of his symptoms. He was able for several years to make a fairly good academic adjustment at public school. His symptoms were tolerated by the teachers, but he was the butt of ridicule from the other students. He avoided athletic activities, with the exception of swimming, and almost completely avoided social activity outside the schoolroom. He felt selfconscious, and feared embarrassment because of his symptoms and the obesity which developed after the onset of his symptoms. He left school after the tenth year because of increased symptoms, lack of interest and poor grades. The next year he attended an industrial high school, but left in midyear because of the frequency of his narcolepsy symptoms. He then obtained a position as a shipping clerk, but gave it up for the same reason after a month. A job as a delivery truck driver was terminated abruptly when he drove off the road during a diurnal nap. He then enlisted in the Navy, over the objections of his mother, shortly after his seventeenth birthday. His symptoms continued to be a daily source of concern and embarrassment, but he managed to complete recruit training. Later he went to an electronics technician school and was graduated in the top of the lower third of the class in spite of his symptoms. After his special schooling he was assigned duty aboard a transport ship. His symptoms persisted and he became increasingly apprehensive that he might have an episode at some crucial moment while on duty. In spite of this concern, he and his division mates managed to conceal his symptoms for over a year, and it was not until after he went home on leave and was shown a magazine article on narcolepsy by his mother that he made his difficulties known to his ship's medical department.

Two nights before the second interview the patient had a prolonged atypical episode of recurrent cataplexy while attending a movie by himself. He estimated that the total experience must have lasted about an hour, during which he had four or five episodes of hypotonia, with some decreased awareness of his surroundings. Each episode was estimated to have lasted about five minutes. He stated that it had been a "crummy movie," to which he had been paying no attention, and added that his episodes of cataplexy while sitting down were almost never in response to an apparent sudden emotion. In addition to reporting the above experience, the patient utilized the second interview to review the feelings he had expressed in the first interview in relationship to other people because of his symptoms. He also elaborated on his change in mood and his current feeling of being more animated and more alert to the people and activities around him.

The patient flew home over the weekend prior to the third and fourth interviews (fourth week without medication), and in those interviews he explored some very significant experiences which took place during that weekend. He was very enthusiastic about how well he had felt over the weekend. He had been able to stay

up very late Saturday night without falling asleep, and his mother had been quite impressed with how lively and wide awake he was. Saturday night his mother took him to a dance. His step-father was not included in this activity. At the dance they met a man who was introduced to the patient as a childhood friend of his mother. He also met the man's 16 year old daughter, Anne. The patient and Anne were immediately attracted to each other. They danced and talked all evening. He took her home and they talked and "necked" until very late. The next day it became apparent to him that his mother had purposefully met Anne's father at the dance and that they were very much interested in each other. His mother and step-father had been having increasing financial differences of opinion. The step-father had decided to take his half of the family resources and return to Italy. His mother planned to obtain a divorce and was thinking of marrying Anne's father. The weekend brought many new feelings to the patient. Some were new and pleasant, and others were old and unpleasant feelings that he had never before recognized in himself. While sitting and waiting for his plane when his mother took him to the airport to return to the hospital, he had an episode of hypotonia and then a narcoleptic attack lasting about five minutes. In the third and fourth interviews he was able to ventilate openly his hostility to his step-father, and was able to express some negative feeling toward his mother in the form of criticism for marrying the step-father and also for having a relationship with another man while she was still married to him. His feelings toward Anne were new and exhilarating but also anxiety-producing. Thoughts of marriage, finishing high school and going to college crossed his mind. He was proud of Anne because, after the sudden death of her mother several months previously, she had taken over the care of her four younger siblings. He spoke with pride of his own siblings and their growing up to be good.

On the last day of the four weeks without any medication the patient was again given a battery of psychologic tests. Extended Recall Bender Gestalt, Bender Gestalt and Recall Bender Gestalt tests gave much the same findings as the previous Bender tests. Difficulty in expressing affect and the need to release hostile affect continued to be apparent. The Extended Recall Bender evidenced repression of castration anxiety and attempts to inhibition dependency needs.

At the end of the four weeks of no medication the patient was again placed on placebo medication, one tablet three times a day, for a period of two weeks. The weekly interviews during that period reflected his increased capacity for affective expression and increased zest for living. He wrote to Anne almost daily, and he was amazed at his ability and desire to do so. At the end of this two week period he again flew home. While going to sleep the night before his departure he had an episode of hazy awareness of his surroundings, accompanied by an inability to move his muscles. This episode was followed by sleep but was estimated to have lasted 15 minutes. The weekend was everything he had anticipated. Most of the time was spent with Anne. They stayed up late, laughed and played together, and decided that they must be in love. He realized that he felt sexually attracted to Anne and she to him.

The patient was then placed on 5 mg. of Dexedrine Sulfate and 32 mg. of amobarbital three times a day for two weeks. During those two weeks he continued to explore the new-found facets of his personality and the world around him, and plans were made for return to duty. He was well motivated for return but was able to express some apprehension that his symptoms might recur after he returned to duty. He was also able to express a dread of returning to a ship for duty if such duty would prevent weekend trips home to visit Anne.

After the Dexedrine Sulfate and amobarbital medication was discontinued the patient was given a final battery of psychological tests. The Extended Recall Bender Gestalt, the Bender Gestalt and the Recall Bender Gestalt findings were essentially

as they had been before, as were the Figure Drawing findings. The Rorschach test evidenced some decrease in constriction and some increase in affective spontaneity. The content of his responses was for the most part unchanged.

When the medication was discontinued the patient complained of decreased energy and fatigue in the late afternoon, and questioned his ability and readiness to return to duty. He wanted to go on leave because he had received a letter from Anne stating that she was overburdened with child care and housework, and that her father had physically mistreated her. In order to combat this development the patient was placed on Dexedrine Sulfate, 5 mg. three times a day. Additional attention was given to helping him work through termination and return-to-duty feelings and his concern about Anne. He was then returned to duty, with instructions that he should return to the hospital if he had further symptoms. A later inquiry revealed that he had been assigned to duty aboard a destroyer. An inquiry at the end of six weeks revealed that his ship was in port and that he was still assigned.

Our observations and treatment of this patient have been included in some detail because they seem to us to be in agreement with other clinicians, already referred to, whose observations and therapeutic efforts indicate that the narcolepsy syndrome in some instances has a psychogenic etiology. The proof is not absolutely conclusive, but there are certain aspects of the total picture of this patient that are impressive. One was the change that came over him during the first six weeks of our structured observation and treatment period. In spite of the shifts from medication to no medication, he made great improvements in his manner of reacting and relating, without return of the symptomatology as it had existed prior to hospitalization. This is understandable if we assume that the period of medication and freedom from symptoms, along with the protective atmosphere and support of hospitalization, made it possible for him to give up some of that portion of his usual mode of reacting and relating which was secondary to his feelings about having narcolepsy symptoms. Such a change was a significant one in that it made for a much better self-awareness during the second six week period, when an effort was being made to help him recognize, express and cope with some of his previously repressed feelings. During the second six weeks there was little relationship of symptoms to the presence or absence of medication. The timing of the symptoms appeared to signal a need for strong repression of feelings which were unacceptable to consciousness at the time. The results of psychologic testing indicate little if any real change in his personality structure during his hospitalization, but that fact is not to deny that he did make important steps toward relating and adjusting more comfortably in the present. Those steps have justified our efforts, even though the psychologic test results may mean that a potential to utilize the symptoms of the narcolepsy syndrome persists.

Summary and Conclusion

This paper developed from the authors' having questioned the concept of idiopathic narcolepsy. The staff conference history of a patient with rather typical idiopathic narcolepsy is presented. As a background for the authors'

original question, the history of narcolepsy and the current concepts of symptomatic and idiopathic narcolepsy are presented. Idiopathic narcolepsy, as a valid clinical concept, is discussed and questioned. The study of the patient whose history was presented at the beginning of the paper is included in some detail as a verification of the authors' belief that a narcolepsy syndrome should not be considered to be idiopathic unless the diagnosis is arrived at by the inclusion of a search for psychogenic etiology in the study of the patient.

SUMMARIO IN INTERLINGUA

Le presente articulo ha resultate ab le facto que le autores se videva obligate a stipular le questionabilitate del traditional concepto classic de narcolepsia idiopathic. In preparation del subsequente discussion del natura de narcolepsia le articulo comencia per reportar satis detaliatemente un conferentia de personal concernite con le historia de un patiente mascule de 20 annos de etate qui presentava omne le componentes del syndrome de narcolepsia. Isto es sequite per un revista historic del complexo de symptomas e un breve presentation e discussion del varie theorias relative al origine de narcolepsia symptomatic e etiam del si-appellate narcolepsia idiopathic. Un revista del litteratura indica, si le autores interpreta lo correctemente, que narcolepsia idiopathic es un morbo functional, que non excede nostre poteres de comprension e que non es disproviste de un psychopathologia demonstratibile. Postea le autores presenta in detalio lor studio e lor tractamento del patiente cujè historia esseva delineate al initio del articulo. Illes include lor observationes de character neurologic, clinico-psychologic, e psychiatric pro justificar lor conviction que un syndrome narcoleptic non debe esser classificate como idiopathic usque un tal diagnose es corroborate per le resultatos del tentativa de establir un etiologia psychogenic.

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DUODENAL LOOP CHANGES IN POSTERIOR PENETRATION OF DUODENAL ULCER*

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The diagnosis and treatment of gastrointestinal disease is enormously influenced by the findings of the trained roentgenologist. In duodenal ulcer particularly, the clinician generally relies greatly on the roentgen findings. The ulcer complications of hemorrhage, obstruction and acute perforation frequently give rise to roentgen findings which are of decisive value in pinpointing the diagnosis.

Chronic posterior perforation of a duodenal ulcer, though a fairly common occurrence, more often than not is first diagnosed on the surgical table. Only rarely does the roentgenologist suggest this diagnosis before surgery. For some time we have been interested in this ulcer complication, and have carefully observed the duodenal loop on roentgenograms for possible significant changes. We now believe that careful evaluation of the duodenal loop on routine gastrointestinal roentgenograms will frequently enable the roentgenologist to suggest this possibility to the clinician. This diagnosis becomes important in clinical management, since surgery will have more to offer the patient than a medical regimen.

The following reports illustrate the roentgen findings in cases of duodenal ulcer which, at surgery, showed either a penetration into the pancreas or a dense mass of adhesions binding the posterior duodenal bulb to the pancreatic bed. The reports are intentionally brief, with only pertinent data presented.

Case Reports

Case 1. This 60 year old white woman, when examined in 1950, had been having epigastric distress, heartburn and occasional vomiting spells for about six years. In recent months the symptoms had been increasing in severity; the epigastric pain frequently radiated through to the back. Roentgen studies on January 10, 1950 (figure 1A), revealed a severely deformed duodenal bulb, with distorted folds, but no definite ulcer crater could be demonstrated. The duodenal loop was slightly irritable but otherwise not unusual. The roentgen diagnosis was chronic ulcerative disease of the bulb, without demonstrable crater.

On stringent medical management the patient improved for a few months. The symptoms then recurred, more severe than before with the penetrating backache more persistent and annoying. A repeat roentgen study on May 22, 1950 (figure 1B), showed greater deformity of the bulb, without a clear-cut crater. The proximal half of the duodenal loop seemed to bulge slightly posteriorly (figure 1A), and the inner aspect had lost the usual serrations, now presenting a smooth appearance. The inner portion of this loop segment also appeared a little stiff fluoroscopically.

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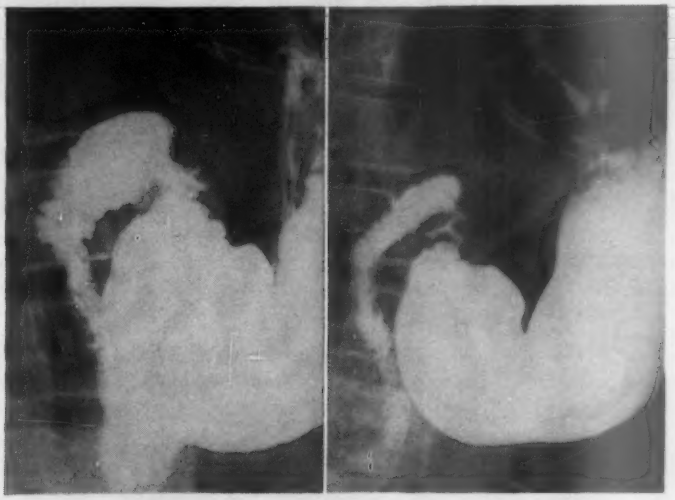
The roentgen findings were thought to represent possible swelling of the pancreas from ulcer penetration into the pancreatic tissue. Surgery seemed indicated, and the posterior penetration into the pancreas was found. Because this segment of the pancreas was quite hard, a partial pancreatectomy was performed, together with a subtotal gastrectomy. Clinically, the patient has been in good health since surgery.

Case 2. A 24 year old white woman had been suffering from recurrent duodenal ulcer symptoms since the age of 12. At that time, a roentgen diagnosis of duodenal ulcer was made. Under medical management she had many comfortable periods, but with frequent clinical flare-ups. For a few months prior to her hospitalization in 1948, the epigastric pain, heartburn and vomiting attacks had increased in severity. Occasionally the epigastric pain radiated through to the back. She had lost 10 pounds in the last three months. A few weeks previously, roentgen studies at another hospital showed a deformed bulb without a crater.



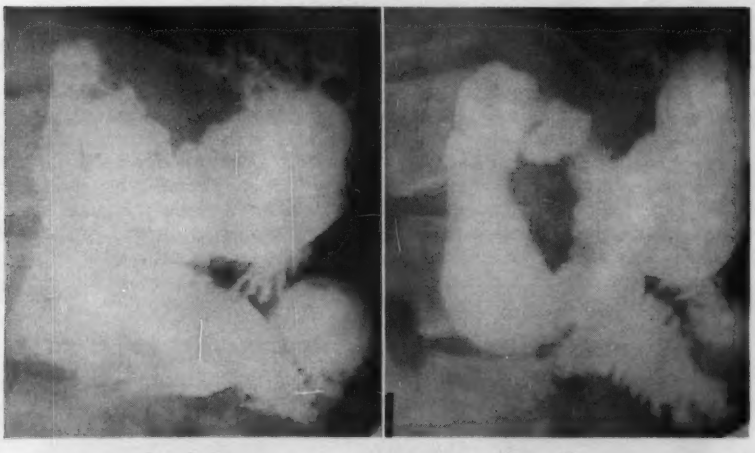
A B

FIG. 1A. *Case 1.* January 10, 1950. B. May 22, 1950. There is a loss of serrations on the inner aspect of the proximal descending loop. The loop also appears to be pushed slightly posteriorly (arrow).

X-ray studies on March 24, 1948 (figures 2A, 2B), revealed a deformed bulb, with a suspicious crater on the lesser curvature aspect. The upper half of the descending duodenal loop seemed stiff, with a straightened inner border and with absence of the usual mucosal serrations. The loop was distensible. These loop findings were considered suggestive of posterior penetration, with possible involvement of the pancreas. Surgery was deemed advisable and was performed.

The ulcer was found adherent to the pancreas, with some penetration into the pancreatic tissue. A thin sliver of the pancreas containing the ulcer was excised and a subtotal gastrectomy performed. Striking clinical improvement ensued. The patient has gained weight and there have been no further clinical symptoms.

Case 3. A 52 year old white male had an ulcer history dating back 22 years. At age 30 a roentgen diagnosis of duodenal ulcer was made, and for a few years relief was obtained from medical management. From then on he was continually ill, with

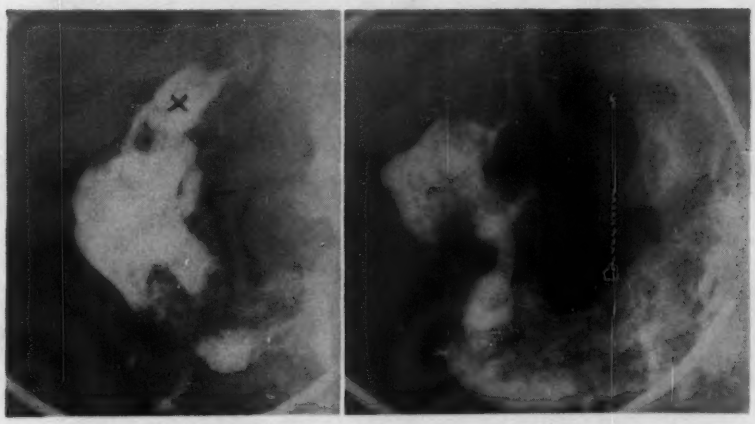


A B

FIG. 2A and B. *Case 2.* Note smoothed contour of the descending duodenal loop.

abdominal pain, weight loss and poor appetite. Many hospitalizations and x-ray studies uncovered only a slightly deformed bulb without crater. Psychiatric care was advised and was given for three years, with only fair results. The severe abdominal pain drove him to the use of narcotics, with eventual addiction. A prolonged stay at a Public Health Service hospital was necessary to break the addiction. At least 15 gastrointestinal series in the last 10 years all indicated a somewhat deformed bulb, without a crater.

In 1947, at the time of the x-ray shown in figure 3, the patient was very thin, and suffered from repeated attacks of severe abdominal pain, with radiation straight through to the back. He had accepted his suffering as a psychiatric illness. The



A B

FIG. 3A and B. *Case 3.* Arrows point to long ulcer tract, extending posteriorly into pancreas. The proximal loop (marked x) is elevated, with loss of mucosal pattern.

films (figures 3A, 3B) demonstrated relatively little bulb deformity, but the distal bulb and proximal loop were elevated and distorted, and showed abnormal mucosal folds. With compression, a tract of barium could be seen arising near the base of the bulb, extending upward and posteriorly into the region of the elevated proximal

FIG. 4. *Case 4.* Note loss of valvulae conniventes on inner margin of the descending duodenal loop.

loop. A diagnosis was made of chronic penetrating duodenal ulcer, probably into the pancreatic bed. This was confirmed at surgery, and a partial pancreatectomy and subtotal gastrectomy were done. Since surgery he has been completely rehabilitated, recovering normal weight and good health.

Case 4. A 45 year old white woman was hospitalized in 1954. For the last six years she had been suffering from heartburn and epigastric pain. A roentgen diagnosis of duodenal ulcer had been made in 1950. Until 1952 she was moderately comfortable under medical management, but gradually the pains became more severe and more frequent. At times the epigastric pains "went straight through to the back." Medication and diet resulted in a smaller measure of relief than formerly. Roentgen studies on May 22, 1952 (figure 4), disclosed a scarred and deformed bulb, but no niche could be demonstrated. The proximal limb of the duodenum showed effacement of the valvulae conniventes on the inner border, with a stiffened appearance of this segment. A roentgen interpretation of chronic duodenal ulcer was made; the loop

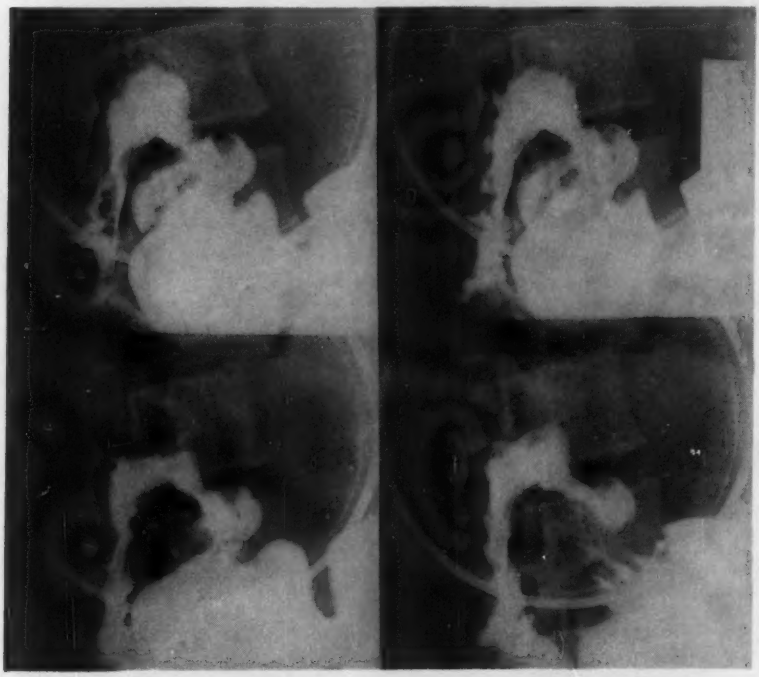


FIG. 5. *Case 5.* Compression seriogram. Note persistent effacement of inner serrations of descending duodenal loop.

alterations suggested the possibility of chronic posterior extension into the region of the pancreatic bed. Surgery was advised but was refused.

During the next two years, in spite of a rigid ulcer regimen, there were repeated attacks of epigastric pain, often associated with backache, and a 15 pound weight loss. Because of increasing discomfort, the patient consented to surgery.

Upon surgical exploration a crater about 0.5 cm. in diameter was found on the posterior aspect of the bulb, penetrating into the pancreatic bed. Considerable fibrosis and many thick adhesions were found binding the bulb to the pancreatic bed. A subtotal gastrectomy without removal of the ulcer was performed. Since surgery, there has been a complete disappearance of the ulcer symptoms and the backache.

Case 5. A 35 year old white carpenter was hospitalized in March, 1954, because of abdominal pain. He had been told five years previously that he had a duodenal ulcer, but with limited medical management had been fairly comfortable until 1952. At that time he was hospitalized because of epigastric pain and vomiting. X-ray studies revealed a deformed bulb with a large crater. Attention was called to the changes in the proximal loop, and the possibility of posterior penetration into the pancreatic bed was suggested. However, since improvement ensued under medical management, surgery was not suggested. Though never entirely symptom-free, the patient had remained moderately comfortable until two weeks before the present hospitalization. Since then, he had experienced gradually increasing epigastric pain, with some food and milk relief. On a number of occasions vomiting alleviated the pain. No backache was experienced. His appetite was rather poor, and he had lost about five pounds during this two week period.

The roentgen studies on April 3, 1954 (figure 5) revealed an active crater, smaller than in 1952, but the bulb was more deformed. The inner aspect of the proximal descending loop was again definitely abnormal, with a smooth inner border and effacement of the valvulae. The contour of this segment was smooth and stiff. Once more the findings suggested to us the likelihood of posterior penetration into the region of the pancreas.

On the strength of the roentgen findings and the inadequate response to routine medication and diet, surgery was advised and performed. Surgical exploration on April 10, 1954, disclosed ". . . duodenal ulcer on the posterior wall, penetrated and adherent to the head of the pancreas. The crater was about five eighths inch in diameter, and about three sixteenths of an inch deep. The duodenum was markedly edematous." Extensive periduodenal adhesions were noted. The head of the pancreas was firm and edematous, with thickening of the capsule.

The ulcer was excised from the posterior wall of the duodenum, but not from the head of the pancreas. Subtotal gastric resection with gastrojejunostomy was performed.

Case 6. A 34 year old white male was hospitalized in May, 1953, with severe epigastric pain for five days. This had persisted without much relief from medication. No back pain was experienced. Seven years previously, similar clinical complaints had led to an x-ray diagnosis of duodenal ulcer. The epigastric pain, with food relief, became a common story with him; repeated x-ray on several occasions showed persistent bulb deformity, with active craters.

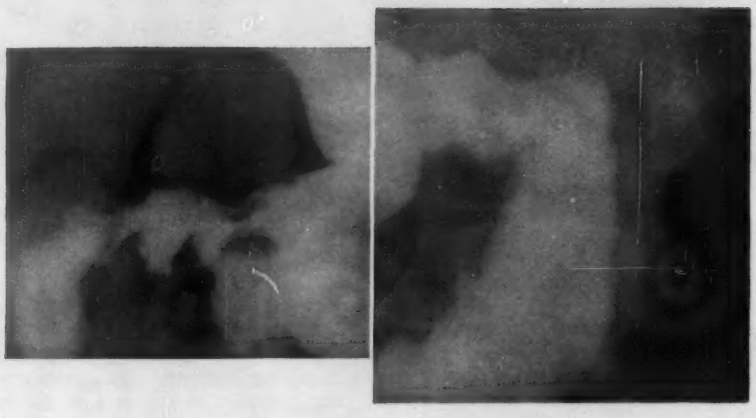
Roentgen studies on May 21, 1953 (figure 6), demonstrated a deformed bulb, with a posterior projection interpreted as either an ulcer or a pseudodiverticulum. There was definite loss of normal valvulae conniventes on the inner surface of the proximal descending duodenal limb, with a smoothed contour. The mucosal folds were coarsened and irregular.

At surgery there was a mass of adhesions around the pancreas and second portion of the duodenum, with heavy scar formation around the ulcer area on the posterior bulb.

Case 7. A 36 year old white man was admitted with a 15 year history of epigastric pain with food relief. A definite x-ray diagnosis of duodenal ulcer had been made five years before this hospitalization. Until two years ago, medical management had kept him fairly comfortable. During the last two years, however, the epigastric pain had become more persistent, requiring increased medication and a stricter diet for comfort. During the last year, radiation of the pain to the back had been experienced. There had been a five pound weight loss during the last month.

X-ray studies on July 12, 1954 (figure 7), revealed a contracted, irritable, deformed duodenal bulb, with suspicion of a crater. The first portion of the descending

A



B C

FIG. 6A, B and C. *Case 6.* The coarsened mucosal folds are demonstrated in A. Note the smooth borders of the descending loop in C and D.

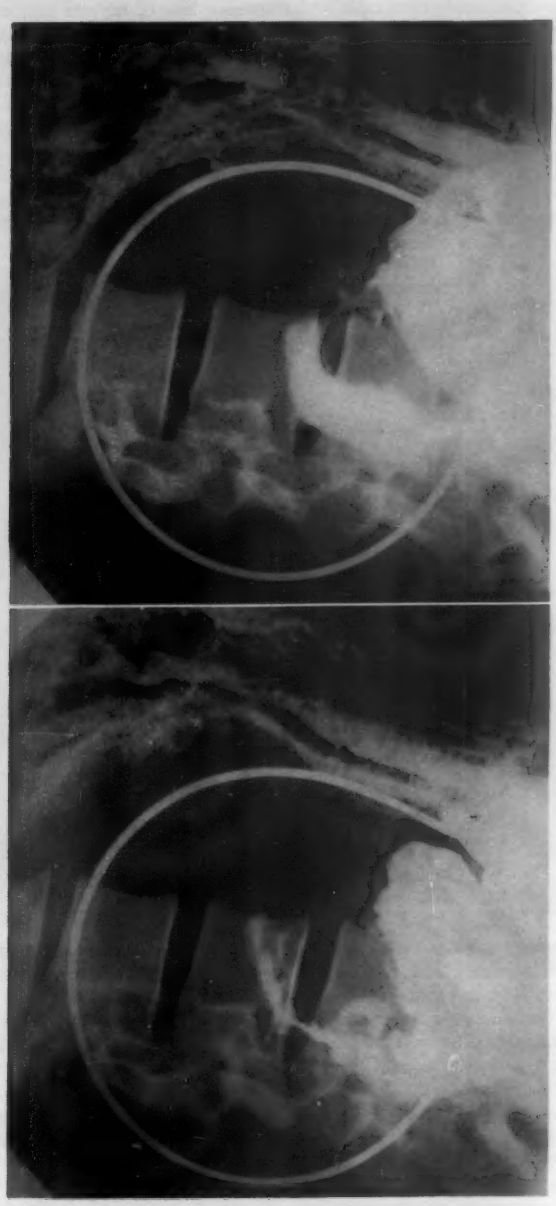


FIG. 7. *Case 7.* The descending duodenal loop has lost its normal mucosal appearance. The inner border is smooth.

duodenal loop was somewhat irritable and showed a loss of normal mucosal serration when distended or contracted. This segment also appeared a bit stiffened. These loop changes were considered suggestive of posterior penetration into the region of the head of the pancreas.

At surgery a dense mass of adhesions bound the bulb and proximal loop to the pancreas. No active ulcerations could be palpated. A subtotal gastrectomy was carried out.

Case 8. A 53 year old white male was hospitalized on February 7, 1954, because of a bleeding duodenal ulcer. The ulcer history dated back seven years, at which time he had been treated by diet and medication and had remained symptom-free for two years. An episode of bleeding then supervened, which subsided under

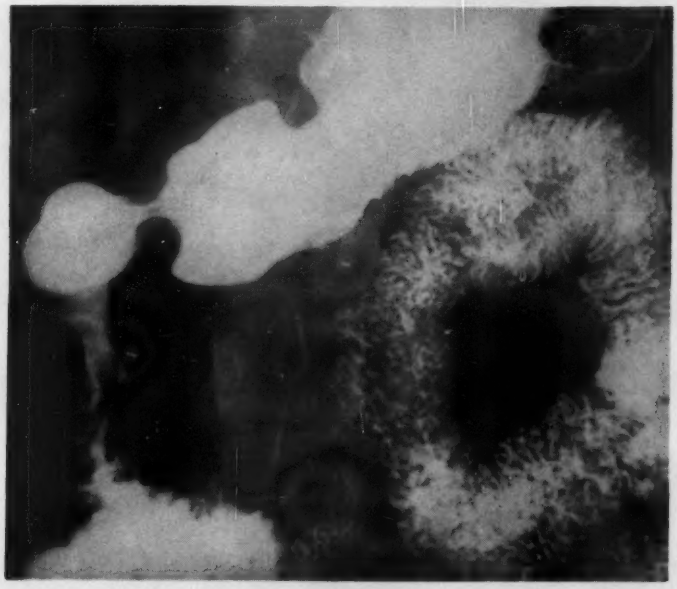


FIG. 8. *Case 8.* The descending duodenal loop (proximal) reveals thickened folds and loss of valvulae conniventes.

conservative management. Until five days prior to this admission he had remained quite well; hematemesis and melena led to this hospitalization. There were only slight epigastric pain and tenderness at the time of admission.

Roentgen studies revealed a small deformed and irritable bulb, with a small barium collection near the apex which was thought to be a crater. The proximal portion of the descending loop (figure 8) showed a loss of the usual mucosal serrations on its inner border. The inner edge of the loop was smooth and appeared stiff. The mucosal folds were thickened and coarsened. At surgery the ulcer penetrated into and was adherent to the pancreas. It was necessary to shave the ulcer from the pancreas, and this was accomplished after some difficulty.

Case 9. A 35 year old white male was hospitalized on January 30, 1955, because of epigastric pain, heartburn and vomiting. A history of duodenal ulcer dated back 11 years. He had had surgery for an acute perforation of a duodenal ulcer

eight years previously. Since then he had been subject to epigastric pain, nausea and occasional bouts of vomiting. During the last few months the pain had been more severe and less responsive to diet and medication. No back pain was elicited in the history. In the last year there had been a 10 pound weight loss. His admission was for the purpose of initiating rigid medical therapy.

Roentgen studies on February 1, 1955, disclosed a spastic, deformed pyloroduodenal area with a small crater. "The descending duodenal loop seems somewhat stiff and rigid, with poorly delineated mucosal folds, especially on the inner aspect of the loop. Moreover, on the lateral-oblique films, the descending loop appears to be pushed posteriorly slightly. . . . We suspect that a posterior penetration with either

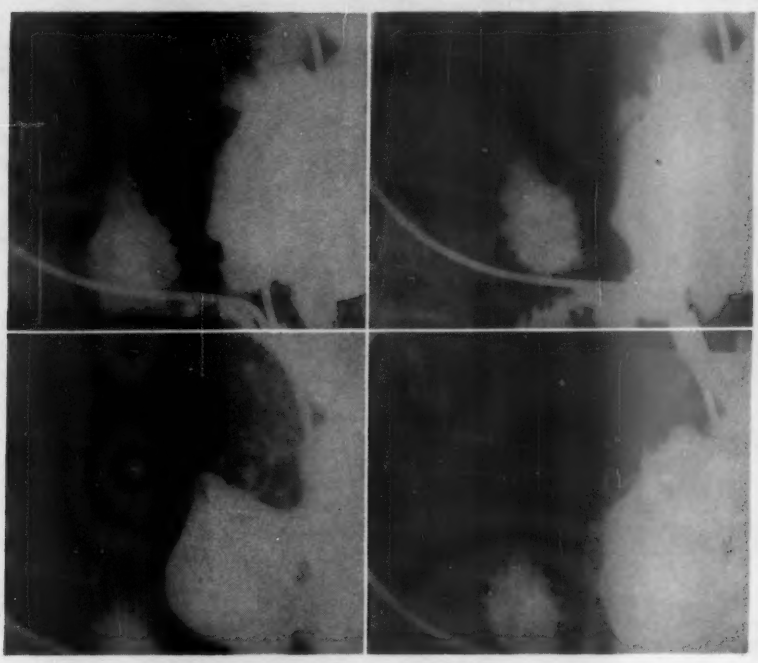


FIG. 9. *Case 9.* Compression seriogram. The proximal descending duodenal loop is irritable, with coarsened folds and loss of valvulae conniventes.

adhesions around the second portion of the duodenum or actual penetration into the pancreas may be responsible for the loop changes." (See figure 9.)

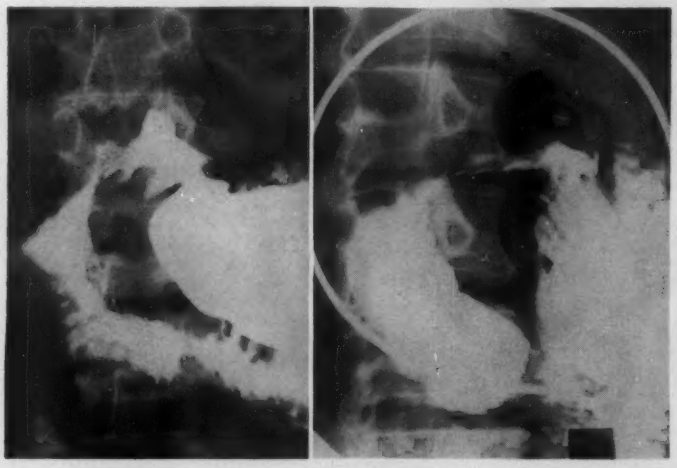
Surgery on February 2, 1955, disclosed a scarred, deformed bulb, with a dense mass of adhesions binding the posterior bulb and proximal loop to the pancreas. A subtotal gastrectomy was performed; the bulb could not readily be freed from the pancreas.

Case 10. A 31 year old Negro male was hospitalized on April 2, 1953. For three months he had been suffering from epigastric pain after meals, relieved somewhat by food or alkalis. During the week preceding hospitalization the pain had become sharper and more persistent, radiating directly through to the back. Daily vomiting spells ensued, and he had lost about 35 pounds in the last three months. Except for

tenderness in the deep epigastrium, physical examination was essentially negative. Laboratory studies, including serum amylases, were within normal levels.

X-ray findings on April 23, 1953 (figure 10), disclosed a deformed bulb, narrowed in its mid-portion, but no clear-cut crater could be demonstrated. The descending loop showed a constant loss of normal mucosal serration on its inner border, from the tip of the bulb to the third portion. This was most marked in the proximal portion of the descending limb. This limb also appeared slightly displaced posteriorly. These findings were considered strongly suggestive of posterior penetration of an ulcer into the pancreas. Clinically, the gastroenterologist also felt that the symptoms suggested posterior perforation. Surgery was advised but refused. Under rigid anti-ulcer therapy the patient improved and was discharged.

Although the patient was fairly comfortable during the next two months, no weight gain occurred. Gradually the epigastric pain with severe radiation to the back recurred, requiring hospitalization on August 17, 1953. Roentgen studies



A B

FIG. 10A and B. *Case 10.* April 23, 1953. The inner aspect of the descending duodenal loop is smooth, showing loss of mucosal pattern. The loop also appears to be displaced slightly posteriorly and laterally.

(figure 11) again revealed the deformed bulb with no crater. The changes in the descending duodenal loop were identical with the former findings. The clinician again felt that the clinical findings were strongly suggestive of pancreatitis associated with a posterior penetrating duodenal ulcer. Surgery again was refused, and the patient was discharged after some improvement from rigid medical management.

DISCUSSION

The anatomic relations of the duodenal bulb and loop to the pancreas are shown in figure 12. It is readily apparent that posterior extension of an inflammatory process from the bulb can produce an involvement of the pancreatic head. If the posterior extension does not penetrate beyond the pancreatic capsule, inflammatory masses or adhesions around the bulb and

mesial surface of the proximal portion of the descending duodenal loop could produce the changes in the roentgen appearance of these structures.

Posterior penetration or extension of a duodenal ulcer is by no means a rare occurrence. Bockus,[1] discussing this subject, states: ". . . As an ulcer erodes into the serosa, the latter becomes adherent to a contiguous structure and the erosive process may extend into that organ or tissue. The walled-off perforation is almost always found on the posterior aspect of the stomach or duodenum, and the ulcer base is usually fixed to the pancreas, liver, or

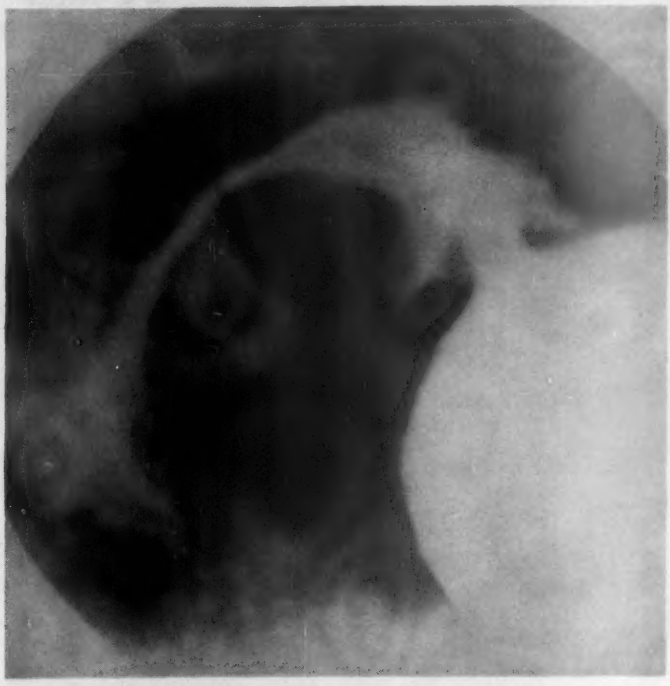


FIG. 11. *Case 10.* August 17, 1953. The changes in the proximal portion of the descending duodenal loop are as striking as four months previously (figure 10A and B).

gastro-hepatic omentum. . . . Walled-off perforations . . . comprise approximately 25% of the group of intractable ulcers not responding satisfactorily to medical treatment." A localized or segmental chronic pancreatitis may result from a peptic ulcer's invading the pancreas. It is second in frequency to disease of the biliary tract in the etiology of pancreatitis.[2, 3] None of the writers on the subject discusses any roentgen signs of posterior penetration.

Clinically, posterior penetration of a duodenal ulcer may be suspected from the history, symptoms and course of the patient with duodenal ulcer. Generally there is a fairly long history of ulcer symptoms, with progressive

difficulty in management, as far as obtaining a symptom-free patient is concerned. Often, backache becomes a prominent symptom; the ulcer pain-food rhythm may be altered. Repeated and more frequent flare-ups of ulcer symptoms are encountered. Too often, however, the poor response to medical management will be laid at the doorstep of the patient, with dietary indiscretions or psychic tension shouldering the responsibility.

The summary of our findings in the reported series (table 1) indicated that nine of the 10 patients had an ulcer history of over five years; in four the history was over 10 years; only in one patient was a short ulcer story obtainable. Seven of the patients were men. In four a poor response to medical management was encountered, in three a fair response, in three a

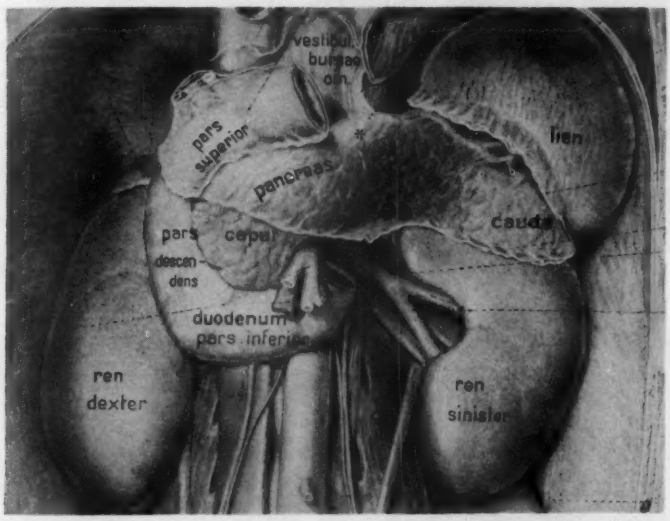


FIG. 12. (After Sabotta.) The intimate relationship of the pancreatic head and the first and second portions of the duodenum is clearly demonstrated.

good response. Backache was a prominent symptom in four patients; it was completely absent in three. It is therefore apparent that the clinical findings alone are not always sufficient to arouse suspicion of posterior penetration. Roentgen findings that would suggest the possibility of this complication should therefore be of considerable aid to the clinician in guiding his management program; certainly surgery offers more in these cases than does medical management alone.

ROENTGEN FINDINGS

When the roentgenogram clearly discloses a deep posterior ulcer, chronic posterior penetration is of course an obvious consideration. This deep posterior crater, however, is usually not seen. A posterior tract was demon-

TABLE 1

Patient	Age	Sex	Duration of Ulcer	Backache	Response to Therapy	Bulb	Crater	Loop Displac.	Loop Smooth Rigid	Distorted Folds	Surgical Findings
1. E. K.	60	F	6 yrs.	++	Poor	Deformed	0	+	+++	±	Posterior ulcer penetrating into pancreas; pancreas hard; partial pancreatectomy
2. E. T.	24	F	13 yrs.	++	Fair	Deformed	++	0	+++	0	Ulcer penetrating into and adherent to pancreas; partial pancreatectomy
3. N. M.	52	M	22 yrs.	±	Poor	Slightly deformed	+++ with tract	++	++	+++	Chronic duodenal ulcer penetrating deeply into pancreas; partial pancreatectomy
4. A. W.	45	F	6 yrs.	++	Fair	Deformed	0	0	+++	0	Crater, posterior wall, penetrating into pancreatic bed. Fibrosis and thick adhesions binding duodenum and pancreas
5. S. W.	35	M	5 yrs.	0	Good	Deformed	+	0	+++	+	Crater on posterior wall, penetrated into and adherent to head of pancreas. Extensive periduodenal adhesions. Pancreatic head firm and edematous
6. M. W.	34	M	7 yrs.	+	Fair	Deformed	±?	0	++	+	Masses of adhesions around pancreas and second portion of duodenum. Scarred bulb
7. F. W.	36	M	15 yrs.	+	Poor	Deformed	±	0	+++	+	Dense mass of adhesions binding bulb and second portion of duodenum to pancreas. No crater
8. M. G.	53	M	7 yrs.	0	Good (bleeding)	Deformed	+?	0	++	++	Ulcer bound down to pancreas; necessary to shave it from pancreatic bed
9. E. C.	35	M	11 yrs.	0	Poor	Deformed	+	+	++	0	Mass of adhesions binding posterior bulb and proximal loop to pancreas
10. C. G.	31	M	3 mos. ???	+++	Good	Deformed	0	+	+++	+	Surgery refused

strated in only one patient of our series (table 1). The bulb deformities alone offer little clue to posterior extension.

From our observations, alterations in the normal roentgen appearance of the descending duodenal loop are significant and, at times, diagnostic of posterior penetration of a duodenal ulcer. The loop changes seen in all of the cases consisted of effacement of the normal mucosal outlines on the inner border of the descending limb, giving this segment a smooth and somewhat stiff appearance. A less constant finding was coarsening of the mucosal folds of this segment of the loop. This was apparent in six of the patients (figures 3, 5, 6, 7, 8, 11). In four the loop was slightly displaced, usually posterolaterally, in one case upward (figures 1, 3, 9, 11). In only one patient was a posterior penetrating ulcer tract demonstrable (figure 3). The loop changes described above always involved the immediate postbulbar area; sometimes the entire descending limb was altered.

Independent observation of these loop changes is to be found in the publication by Gottlieb, Dorfman and Cregg.[7] In 1951 they reported on nine cases of pancreatitis with roentgen changes in the duodenal loop. Four of these cases were due to posterior penetration of a duodenal ulcer. The roentgen changes in the loop of their cases are quite in keeping with our own, and consist of the following: (a) flattening of the valvulae conniventes on the inner aspect; (b) extrinsic pressure on the loop; (c) variable narrowing of the duodenum, accompanied by loss of normal mucosal markings; (d) distention of the proximal duodenal loop due to obstruction of the duodenojejunal junction by an enlarged, firm pancreas.

Pancreatic inflammation secondary to a penetrating duodenal ulcer is apparently of the subacute or chronic type. Acute pancreatitis gives rise to different roentgen findings, not to be confused by those described in our series. A number of writers on the subject [4, 5, 6] have described the roentgen changes in acute pancreatitis. These include elevation of the stomach and transverse portion of the bulb, enlargement of the duodenal loop, atony of the dependent portions of the duodenum, defects in the contour of the duodenojejunal flexure, coarsely feathered duodenal folds, left diaphragmatic limitation, pleural exudates in left chest, ill defined left psoas shadow and even paralytic ileus.

In our early observations we believed the loop changes were due exclusively to inflammatory involvement of the pancreas secondary to penetration of the ulcer. Later cases indicated, however, that periduodenal adhesions from extension of the ulcer beyond the serosa could similarly modify the mucosal picture of the descending loop, especially the postbulbar portion, even though the pancreas itself was not involved. Several cases, not reported in this series, showed similar though less marked loop changes. Each patient eventually required surgery because of poor response to medical management. In each patient evidence of previous extension of the ulcer beyond the serosa was found.

In concluding the discussion, we would like to emphasize the need for constancy in the appearance of the loop changes described in the cases above. The appearance of the loop on a single film may mean little, since peristaltic activity, together with the rapidity of present day roentgen exposures, can produce unusual appearance on a single film. In all the cases reported above, the loop changes were apparent on all the exposures.

Summary and Conclusions

1. Ten cases are presented of chronic duodenal ulcer, with roentgen findings which we consider suggestive of posterior extension of the ulcer into the pancreatic bed or into the pancreas itself.

2. Of the nine cases undergoing surgery, penetration of the ulcer into the pancreas was found in six; in the other three, dense adhesions from posterior extension were found around the bulb and second portion of the duodenum (table 1). These adhesions apparently are responsible for the roentgen changes.

3. The constant roentgen finding of this series was the effacement of the valvulae conniventes on the inner aspect of the descending duodenal loop, giving rise to a smooth and somewhat stiff appearance of this segment. Other changes were the coarsening of the mucosal folds and the postero-lateral displacement of the descending loop.

4. Clinically, there was usually a long-standing ulcer history, with less than good response to medical management. The radiation of the epigastric pain through to the back was a symptom in about half of these patients.

5. Close attention by the roentgenologist to the duodenal loop in cases of chronic duodenal ulcer should prove helpful in suggesting the possibility of chronic posterior penetration. This may be a deciding factor to the clinician in advising surgery.

Summario in Interlingua

Chronic penetration o perforation posterior de un ulcere duodenal es un complication que es usualmente recognoscite solmente durante le intervention chirurgic. Esseva interprendite un minutiose examine de roentgenogrammas con le objectivo de discoperir aspectos de possibile signification pro iste complication. Omne adjuta diagnostic es importante in iste condition, proque in illo le patiente ha multo plus a expectar ab methodos chirurgic que ab le simple tractamento medical.

Clinicamente parlante, le patiente con chronic penetration posterior ha usualmente un satis longe historia de ulcere. Le tractamento medical deveni generalmente de minus in minus efficace si on considera como proposito le liberation del patiente ab su symptomas. Dorsalgia pote esser un symptoma prominente, e il es possibile que un alteration occurre in le rhythmo de ingestion e dolor. Eclosiones subitanee deveni plus frequente e plus difficile a subjugar. Variationes ab iste schema non es infrequente.

Super le base del 10 casos hic reportate, nos conclude que certe signos roentgenologic es satis indicative de penetration posterior in casos de chronic ulcere duodenal.

Alterationes del apparentia del descendente ansa duodenal esseva constatate in

nostre casos. Le obliteration del normal contornos mucosal (valvulas connivente) esseva characteristic de omne le patientes. Isto resulta in un lisie e satis rigide apparentia del margine interior del ansa descendente e pare esser le plus constante e le plus significative alteration. Un "crudification" del plicas mucosal de iste segmento del ansa esseva observate in sex del 10 patientes. Un leve displaciamento del ansa descendente, usualmente in un direction postero-lateral, esseva notate in quatro casos. Le alterationes ansal involveva semper le immediate segmento postbulbar. A vices le integre section descendente esseva alterate. Un tracto ulceric de extension posterior ab le bulba esseva observate in solmente un patiente.

Pro meritar nostre considerar le alterationes ansal como significative, illos debe esser constante. Si on examina un sol roentgenogramma, un ansa que es normal pote accidentalmente presentar se in stato contrahite e simular un transformation lisie de su margine interior. Un adequate studio roentgenographic del vias gastro-intestinal elimina le erronee interpretation del aspecto del ansa.

Nos opina que le causa anatomico-pathologic de iste alterationes del ansa es (1) le extension del ulcere in le pancreas, con resultante chronic pancreatitis localisate, o (2) adhesiones periduodenal ab le penetration chronic, con extension del adhesiones al portion postbulbar vicin del descendente ansa duodenal.

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"PLATELET" THROMBOSIS IN LEUKEMIA *

By KJELD O. HUSEBYE, M.D.,† J. M. STICKNEY, M.D., and WARREN A. BENNETT, M.D., *Rochester, Minnesota*

CAPILLARY thrombosis is observed in a number of conditions. Extensive involvement has been reported in a variety of diseases, such as rickettsial infections,[1] disseminated lupus erythematosus,[2-4] periarteritis nodosa,[5] malignancy,[6] aplastic anemia[7] and thrombotic thrombocytopenic purpura. The pathogenesis is as yet undetermined.

Moschcowitz[8] was the first to report an instance of thrombotic thrombocytopenic purpura; this he did in 1925. He believed the thrombi consist of agglutinated erythrocytes, and pointed out that there is no evidence of primary vascular disease. Altschule[9] ascribed the lesions to damage to the vascular endothelium, with secondary deposition of platelets. Muirhead and associates[10] reported one case in which there were extensive endothelial proliferation, "platelet" thrombi and simultaneous "glomerulitis."

Gore[11] suggested that the earliest prethrombotic lesion in thrombotic thrombocytopenic purpura is a swelling of the subendothelial hyaline material, followed by rupture of the endothelium, with deposition of platelets on the injured spot and formation of a bimorphic thrombus. Endothelial proliferation and organization of the thrombus would then take place, only to be followed by new depositions of platelets, bringing about thrombocytopenia. Two of his five patients had a leukemoid blood reaction. In most cases reported, a shift to the left, with immaturity, was noted in smears of peripheral blood, but leukemia was ruled out. The clinical picture is rather typical, although not specific for the condition.

MATERIAL AND METHODS

In a study of the kidneys of 110 leukemic patients who came to necropsy at the Mayo Clinic, three were noted to have lesions resembling those described above, under the term "platelet" thrombi. It should be recalled, however, that no test for platelets in fixed sections is specific, and that there still is controversy as to the exact nature of the thrombi. Paraffin blocks were made of formalin-fixed specimens of tissue which were stained by a modified hematoxylin-and-eosin technic. The tissue also was stained ac-

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cording to Mallory-Heidenhain's and Schiff's periodic acid methods, but these procedures gave no additional information.

Case Reports

Case 1. A three year old boy had acute lymphocytic leukemia of 17 weeks' duration. Blood was administered several times, without complications, up to five days before death of the patient.

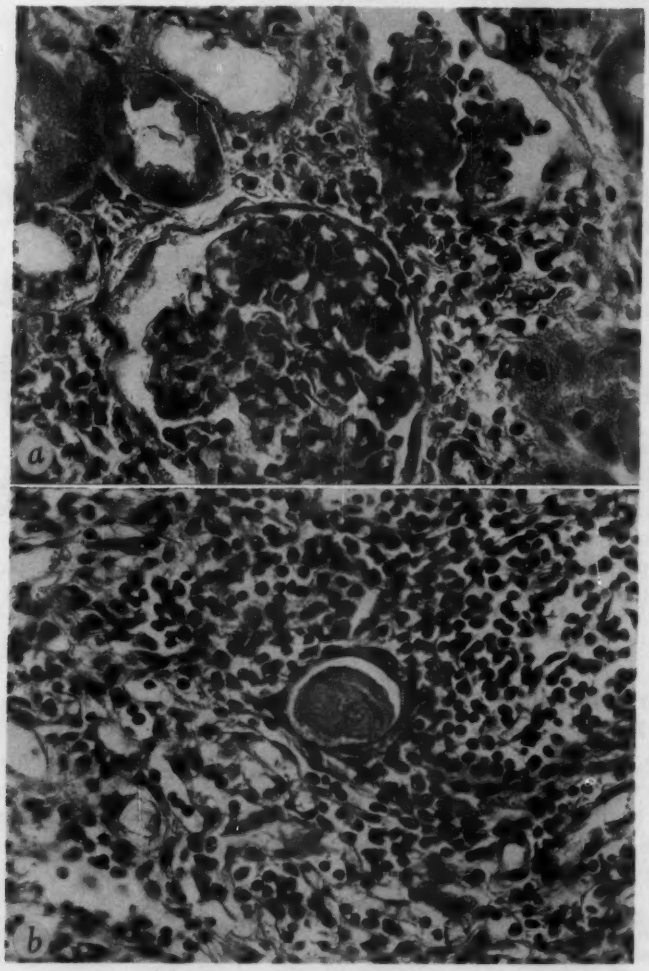

Fig. 1. *Case 1.* Acute lymphatic leukemia in a three year old male treated intermittently with folic-acid antagonists. *a.* Kidney. "Platelet" thrombi in glomerular capillaries, with periglomerular leukemic infiltration (hematoxylin and eosin; × 400). *b.* Thymus gland. Thrombosis in arteriole. Endothelial cell proliferation about the thrombus (hematoxylin and eosin; × 400).

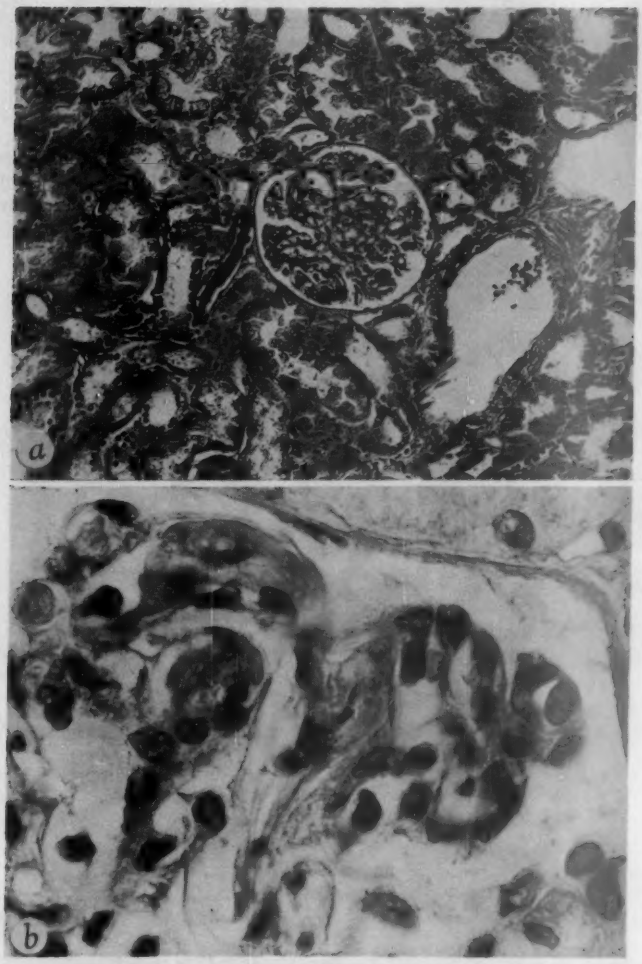

FIG. 2. *Case 2.* Chronic myelogenous leukemia in a 58 year old woman treated with two courses of roentgen irradiation. *a.* Kidney. "Platelet" thrombi in glomerular capillaries and in arteriole. Tubular epithelium intact (hematoxylin and eosin; × 150). *b.* Kidney. Glomerular capillaries plugged with "platelet" thrombi. Normal basement membrane with no endothelial proliferation (hematoxylin and eosin; × 800).

Intermittent treatment with a folic-acid antagonist (aminopterin) over a nine-week period failed to induce a remission. The total dose was 11.5 mg. Treatment was discontinued 10 days prior to the patient's death.

Under the treatment leukocyte counts varied between 1,300 and 25,000 per cubic millimeter of blood. The platelet count decreased temporarily from 62,000 per cubic millimeter to 8,000. Eight days before death of the patient cutaneous hemorrhages developed, while the platelet count was 23,000 per cubic millimeter. Platelets increased to 41,000 the day before death, while the leukocyte count was 250 per cubic

millimeter. Minimal albuminuria was noted. Examination of marrow obtained by sternal aspiration showed it to be very hypoplastic, with very few megakaryocytes.

The condition grew rapidly worse. Fever and a decrease in blood pressure supervened, and the patient died in respiratory failure.

Necropsy revealed marked gastrointestinal hemorrhage. The kidneys were large and swollen (weight, 255 gm.; estimated normal, 115 gm.), with a mottled yellow-and-red surface and bilateral submucosal hemorrhages in the pelves. Leukemic infiltration was minimal. The glomerular basement membrane was minimally thickened, with some epithelial proliferation. The glomerular capillaries were partly

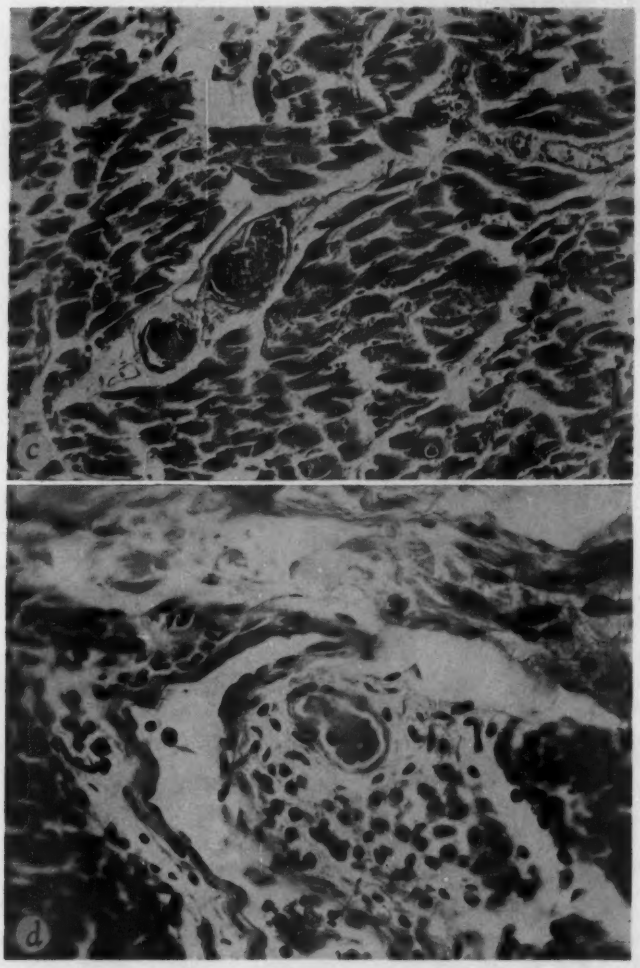

FIG. 2*c*. *Case 2*. Myocardium. "Platelet" thrombi in arterioles (hematoxylin and eosin; × 150). *d*. Skin from the thigh. "Platelet" thrombus in arteriole adjacent to benign nevus (hematoxylin and eosin; × 400).

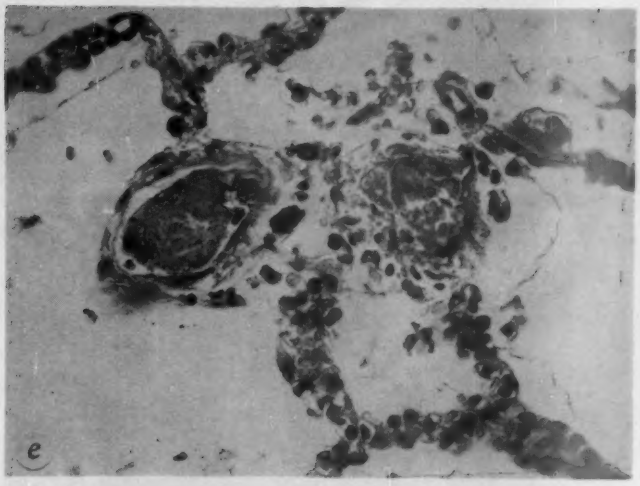

FIG. 2*e*. *Case 2*. Lung. "Platelet" thrombi in arterioles and capillaries. Note endothelial cells adherent to thrombus (hematoxylin and eosin; × 400).

filled with "platelet" thrombi (figure 1 *a*). Occasional erythrocytes were found in the tubules.

Study of other tissues revealed "platelet" thrombi in the capillaries and arterioles of the heart muscle, liver, thymus (figure 1 *b*) and some lymph nodes. A decrease in megakaryocytes was noted in the bone marrow.

Case 2. A 58 year old woman had chronic myelogenous leukemia, discovered seven months before her death. Blood was administered four days and one day before death, and a febrile reaction appeared the first time.

Roentgen irradiation for the leukemia was given in two courses, seven months and one month before death.

Initial leukocyte counts of 275,000 decreased to 12,300 after treatment, but increased again before death to 34,600 per cubic millimeter. Blood platelets decreased from a normal count six months before death of the patient to 30,000 per cubic millimeter four days before death, increasing to 55,000 on the day of death. Sternal aspiration of marrow was not done. Results of urinalysis were repeatedly normal; the last time urinalysis was done was two days before death of the patient.

For 17 days the patient experienced chills and nosebleeds. Extensive ecchymoses were noted three days before death. The blood smear disclosed an acute exacerbation of the leukemia. Respiratory symptoms developed and the patient died from extensive cerebral hemorrhage.

Necropsy disclosed extensive cerebral and subarachnoid hemorrhage. The kidneys were pale and firm (weight, 300 gm.; estimated normal, 315 gm.). Leukemic infiltration was minimal. The glomeruli (figures 2 *a* and *b*) showed no endothelial proliferation, and the basement membrane was normal. Mild epithelial proliferation was seen. The capillary loops were partially filled with "platelet" thrombi which appeared not to be attached to the wall of the vessel. The rest of the lumen was filled with erythrocytes and leukocytes.

The appearance of the tubules was not remarkable; they contained some pigment casts and occasional erythrocytes. Occasional deposits of calcium salts were noted.

Similarly, "platelet" thrombi were found in the arterioles of the kidneys. The arteries did not contain thrombi.

Study of different tissues revealed (figures 2 *c*, *d* and *e*) "platelet" thrombi and occasional mild endothelial proliferation in the arterioles and capillaries of heart muscle, adrenal glands, diaphragm, paratracheal node, subcutaneous tissue (figure 2 *d*), lungs (figure 2 *e*), pancreas, tonsils and right sciatic nerve. Marked leukemic infiltration of sternal marrow, with a decreased number of megakaryocytes, was

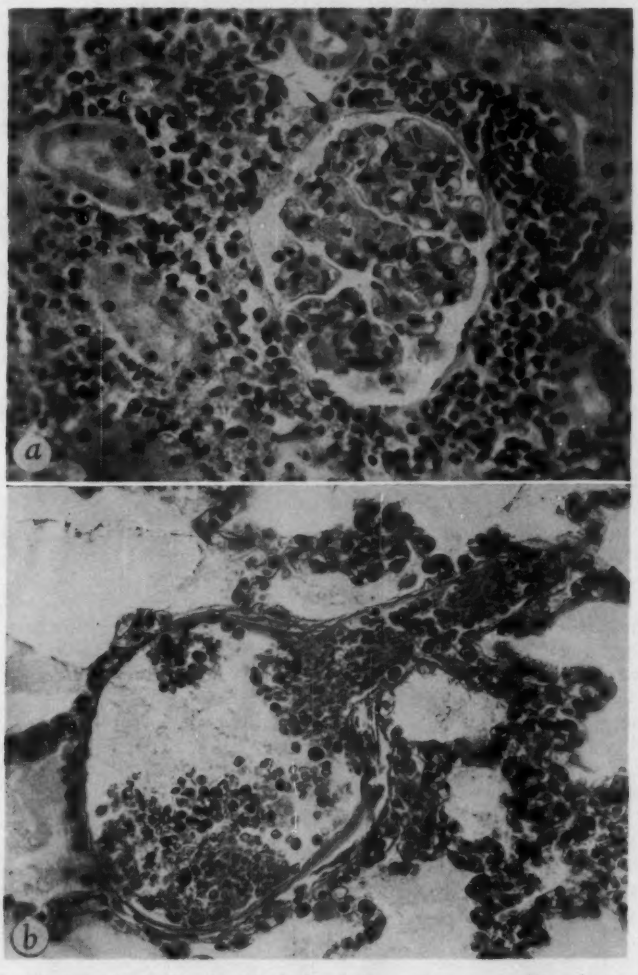

FIG. 3. *Case 3.* Acute lymphocytic leukemia in a three year old male treated with urethane and folic-acid antagonists. *a.* Kidney. "Platelet" thrombi in glomerular capillaries with dense periglomerular leukemic infiltration (hematoxylin and eosin; × 400). *b.* Lung. "Thrombosis" in the branches from small pulmonary artery and in the capillaries in the alveolar wall. The larger vessels were not involved (hematoxylin and eosin; × 300).

noted. One partly organized thrombus mixed with leukemic cells was noted in the myocardium (figure 2 *c*). In another arteriole the occluding mass gave the impression of retraction, with a shrinking away from the wall, forming an endothelial-lined lumen (figure 2 *c*).

Case 3. A three year old boy had acute lymphocytic leukemia of 14 months' duration. Blood was administered several times, without untoward reactions, up to the day before the patient's death.

Three fairly complete but short remissions occurred under treatment with folic-acid antagonists given intermittently for almost 14 months. Urethane was given for one three-week period.

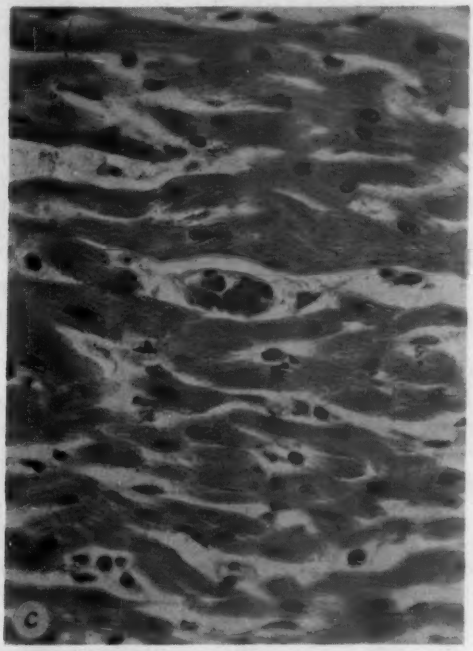

FIG. 3*c*. *Case 3.* Myocardium. "Platelet" thrombus in capillaries (hematoxylin and eosin; × 400).

Leukocyte counts varied between 7,800 and 1,200 per cubic millimeter of blood, and blood platelets initially numbered 69,000 per cubic millimeter. Examination of sternal marrow from the initial aspiration showed a hypoplastic marrow with a decrease in megakaryocytes. Results of urinalysis were normal, but urinalysis was not repeated the last three months before death.

The patient received 1 mg. of aminopterin every day for two months. Massive hemorrhages developed. The day before the patient's death the leukocyte count was 304,000 per cubic millimeter and the platelet count was 11,000 per cubic millimeter. A smear of peripheral blood showed more than 90% stem cells and atypical lymphocytes. The patient became subfebrile and severe respiratory symptoms developed. Death ensued.

Necropsy revealed extensive gastrointestinal hemorrhage and bronchopneumonia. The kidneys were dark red, with mottled purple areas, and peripelvic hemorrhage was present (weight, 305 gm.; estimated normal, 115 gm.). Extensive leukemic infiltration was noted.

The glomeruli (figure 3 *a*) showed minimal endothelial proliferation, with minimal thickening of the basement membrane and mild epithelial proliferation. The capillary loops of the glomeruli were filled with "platelet" thrombi intermixed with a few erythrocytes and leukocytes. The degenerating tubular epithelium exhibited some sloughing, with foci of proliferation. Erythrocytes were found in a few tubules. Hyaline globules and casts were noted frequently.

Study of tissues revealed "platelet" thrombi in the arterioles and capillaries of the lungs (figure 3 *b*), heart muscle (figure 3 *c*), subperitoneal tissue, gastrointestinal tract, bone marrow and lymph nodes. A decreased number of megakaryocytes was noted in the sternal marrow.

Comment

There is no agreement as to the true nature of the capillary thrombosis which we have described. In the presence of thrombotic thrombocytopenic purpura the platelet production is considered either normal or low by some authors. Others, such as Gore, noted increased numbers of megakaryocytes in the bone marrow. However, after the filtering away of the platelets in the capillaries and arterioles, he noted a decrease in platelets in peripheral blood to a level at which he thought extensive hemorrhages were likely to occur.

A decreased number of megakaryocytes was noted in the sternal marrow in our cases. Low blood platelet counts were found at the time of death. Extensive bleeding developed and the patients died rather rapidly. At necropsy a diagnosis consistent with acute leukemia was made. (One had an acute exacerbation of chronic myelogenous leukemia.) The capillaries and arterioles from the different tissues contained "platelet" thrombi of varying age and number, although they were far fewer than in thrombotic thrombocytopenic purpura. The intima of the vessels was relatively unaffected, and the endothelial hyperplasia was considered to be secondary to the thrombotic processes. Occasionally a thrombus was surrounded by flattened endothelial cells. The vascular lesions were extensive enough to contribute to thrombocytopenia. Hemorrhage probably was directly related to the diminished platelet formation and the trapping of platelets in the thrombi. No relationship to the therapy administered or to the degree of leukemic infiltration was demonstrable.

A study of the literature revealed various suggestions as to causation and pathogenesis of this type of capillary thrombosis. It is seen, in the concomitant occurrence of purpura, thrombocytopenia and capillary thrombosis ("thrombotic thrombocytopenic purpura") and in the presence of such conditions as infections, hypersensitivity with biologic false-positive serologic reactions, malignant processes and aplastic anemia. Capillary "platelet" thrombosis with thrombocytopenia, in this paper described as an

accompaniment of acute leukemia, appears to be in many instances a complicating syndrome rather than a disease entity.

SUMMARY

Disseminated "platelet" thrombi were demonstrated at necropsy in two cases of acute leukemia and one of chronic myelogenous leukemia with an acute terminal exacerbation. There was no common etiologic denominator in the three cases, except for the acute phase of the disease.

Although the lesions were far fewer and less extensive than in thrombotic thrombocytopenic purpura, the similarity in symptoms, signs and necropsy findings is pointed out. In contradistinction to the usual descriptions of thrombotic thrombocytopenic purpura, the number of megakaryocytes in the bone marrow in our three cases was decreased.

Roentgen irradiation had been administered to one patient, folic-acid antagonists and urethane had been given to another, while a third patient had received only folic-acid antagonists. The presence of capillary thrombosis was considered to be unrelated to the therapy administered.

Descriptions of the lesions in the literature vary greatly, as do suggestions as to causation and pathogenesis. It is suggested that "platelet" thrombosis with thrombocytopenia, when it occurs simultaneously with other diseases, frequently is a complicating syndrome rather than a disease entity.

SUMMARIO IN INTERLINGUA

Disseminate thrombos "plachettal" esseva demonstrate necropticamente in duo casos de acute leucemia e in un caso de chronic leucemia myelogene con acute acerbation terminal. Il non habeva un commun denominator etiologic in le tres casos, excepte le phase acute del morbo.

Ben que le lesiones esseva multo minus numerose e minus extense que in thrombotic purpura thrombocytopenic, le similitude de symptomas, signos, e constationes necroptic merita esser signalate. In contrasto con le descriptiones usual de thrombotic purpura thrombocytopenic, le numero del megacaryocytos in le medulla ossee de nostre casos esseva reducite.

Roentgeno-irradiation habeva essite administrate a un del patientes. Un altere habeva recipite antagonistas a acido folic e urethano, durante que le tertie habeva prendite solmente antagonistas a acido folic. Nos opina que le presentia de thrombosis capillari habeva nulle connexion con le therapia administrate.

Le descriptiones de iste lesiones in le litteratura varia grandemente, exactemente como le opiniones in re lor causas e lor pathogenese. Nos formula le conception que thrombosis "a plachettas" con thrombocytopenia, si illo occurre in conjunction con altere morbos, es frequentemente un syndrome complicatori plus tosto que un entitate pathologic independente.

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CASE REPORTS

PROGRESSIVE PULMONARY HISTOPLASMOSIS WITH BILATERAL RESECTION AND CHEMOTHERAPY *

By CARL R. HOWSON, M.D., F.A.C.P., LYMAN A. BREWER, III, M.D., F.A.C.S., *Los Angeles, California,* WILLIAM H. OATWAY, JR., M.D., *Altadena, California,* and ELLIOT A. ROUFF, M.D.,† *Los Angeles, California*

PULMONARY histoplasmosis, like pulmonary coccidioidomycosis, may simulate tuberculosis so closely that the differentiation on physical and radiologic examination may be impossible. While comparatively little is known as to the extent of its geographic dissemination, there is good reason to believe that it is much more widespread than has been suspected. Its recognition is therefore of increasing importance.

The case reported here presents several aspects which, to the best of our knowledge, have not yet been mentioned in the literature.

CASE REPORT

A white male, age 38, employed as foreman of an oil well supply company, first consulted a thoracic surgeon (L.A.B.) in December, 1952.

Two years previously a preëmployment film had shown pathologic changes in the apex of the left lung, following which he had been under the observation of the Health Department, and had recently been told he should enter a sanatorium because he had tuberculosis. Numerous sputum tests had failed to reveal tubercle bacilli.

He was advised to have a gastric lavage with culture and guinea pig inoculation for tubercle bacilli, and also a bronchoscopy. Gastric lavage was finally consented to on January 23, 1953, but bronchoscopy was refused.

On February 12, 1953, he was referred (to C. R. H. and E. A. R.) for further study, and gave the following history:

He had had only a very slight cough recently (since reducing his smoking), and raised 1 dram or less of dark mucoid sputum daily. A week previously he had had some discomfort in the left upper chest and had raised flecks of blood for about 24 hours. He was working regularly and felt perfectly well.

Family History: Noncontributory.

Previous Illnesses: Usual childhood diseases. Tonsillectomy as a child. Appendectomy in 1939.

Physical Examination revealed an alert, slender adult male of strawberry-blonde complexion, 6 feet in height and weighing 144 pounds (unchanged in recent years).

Temperature was 98.4° F.; pulse, 80; respiration, 20; blood pressure, 124/88–76 mm. of Hg.

Head and neck were normal.

* Received for publication June 20 1955.

† Unless otherwise stated, the laboratory studies were conducted by R. A. Hammack, M. D. and associates.

The chest showed normal development, with slightly limited expansion over the upper left hemithorax and slight retraction of the left base posteriorly. On percussion there was slight impairment of resonance over the upper left lung. Breath sounds were normal. Fine crepitations were heard near the spine of the left scapula on cough.

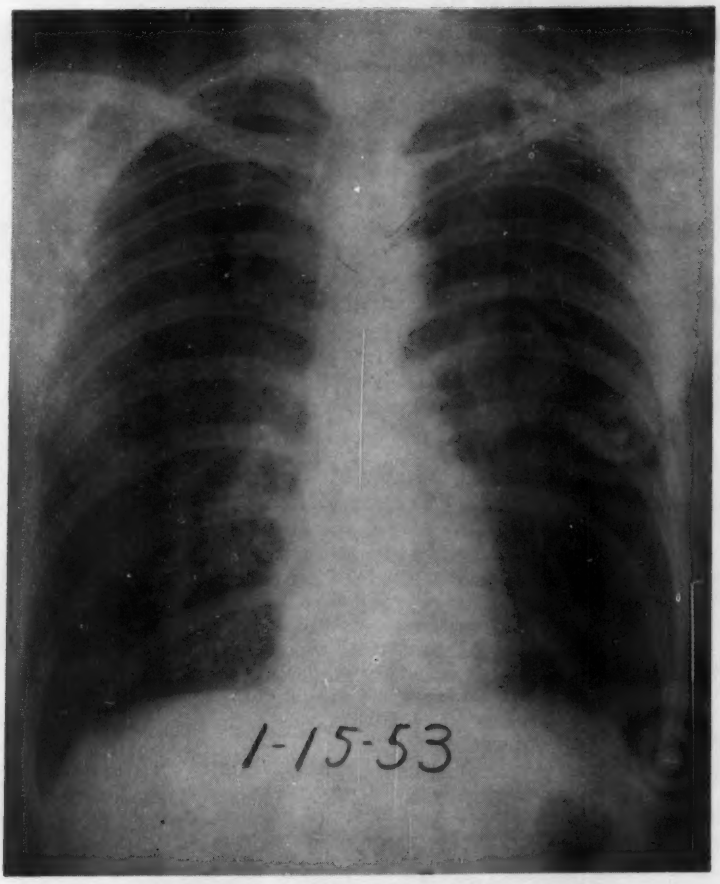

FIG. 1. Infiltration of the left apex with a small cavity.

Cardiac and abdominal findings were normal.

Fluoroscopy showed some impairment of illumination in the apex of the left lung but was otherwise within normal limits.

An x-ray film which had been taken on January 15, 1953, showed fairly dense infiltration in the apex of the left lung with a small cavity (figure 1).

Laboratory Studies: Mantoux test, PPD .0002 mg., was negative; a second Mantoux test, PPD .001 mg., negative; a third Mantoux test six weeks later, PPD .0025 mg., negative; coccidioidin test, 1–100, negative; repeat test six weeks later,

1–10, negative. The gastric lavage done on January 23 was reported on March 23 as negative for tubercle bacilli on both culture and animal inoculation. Gastric lavage for coccidioidomycosis was done on April 4; fresh specimens and culture were reported negative, and on August 15 animal inoculation was reported negative for *Coccidioides immitis*. In the meantime, complement fixation tests and precipitin tests for *C. immitis* were reported as entirely negative. On October 23 the laboratory reported that a guinea pig which had been inoculated intratesticularly at the time of the gastric lavage for *C. immitis* had shown a small nodule in one testicle, histologic sections of which showed a lesion suggestive of histoplasmosis, and culture of the nodule revealed a growth of *Histoplasma capsulatum*. On September 2 a histoplasmin test, 1–100, gave a 2 plus positive reaction, a 1–50 test a 3 plus reaction.

After some delay we were able to assemble his complete x-ray file, and a review revealed the following:

A preëmployment film dated September, 1948, showed a normal chest except for a small, elliptical shadow immediately below the posterior aspect of the left first rib. This had evidently been interpreted as pleural and of no clinical importance, but was very possibly the initial lesion.

The survey film of September 5, 1950, showed infiltration in the left apex extending down to the level of the first costal cartilage and including the trunks extending outward from the left hilum; at the periphery of the first interspace was a shadow suggestive of a small excavation. In the films taken by the Health Department at irregular intervals over the next two years, including that shown in figure 1, no material change was indicated.

A detailed occupational history revealed the following:

He had been graduated from high school in 1934, and two years later was employed by an oil well supply company. In February, 1945, he entered the Merchant Marine. During that summer, while working on a tanker, he made a trip through the Panama Canal to the Philippines, where he remained about 40 days, returning in October. He spent two days on shore in Panama while going through in both directions, and on the return trip spent two days in New Orleans.

Following his release from the service he was sent to Colombia with an oil well drilling outfit in September, 1948, and remained there for approximately one year. His work was supervisory, with no manual labor. The camp was at a low altitude. The food and living conditions were satisfactory, but the climate was extremely humid. Every six weeks he went to Bogota (altitude, 8,600 ft.) for a week. The weather there was always cold, windy and dusty, and he regularly caught cold on the trip. In July, 1949, he developed a severe pain in the lower left chest, aggravated by respiration, cough and movement, and lasting about two weeks. Apart from these illnesses he had felt quite well during the year, and does not remember having any cough in between times. A minifilm taken there on October 10, 1949, showed an exudative-appearing infiltrate occupying the apex of the left lung.

He arrived home from Colombia on October 27, 1949, but did not immediately return to work.

In July, 1950, a preëmployment film was taken, and on the strength of this he was refused employment. In October, 1950, another firm had a preëmployment examination made, including a chest film, and he was accepted for service in Arabia. En route he had an attack of syncope and was sent home. In December, 1950, he was reëmployed by the oil well supply company, in the assembly department. He never noted any special fatigue, and was still working there when first seen by us.

He denied ever having been in the Mississippi or Ohio River Valleys except for passing through on the train and for the two days spent in New Orleans in 1945.

Discussion: In view of the patient's failure to react to repeated Mantoux tests

with increasing strengths of PPD, failure by the Health Department to find tubercle bacilli on repeated examinations, the negative gastric lavage findings by a private laboratory, also failure to find any evidence of coccidioidal infection, coupled with the demonstration by animal inoculation of what was felt to be *Histoplasma capsulatum,* a diagnosis of probable pulmonary histoplasmosis was made. However, because of the extreme rarity of an isolated progressive condition, it was felt that

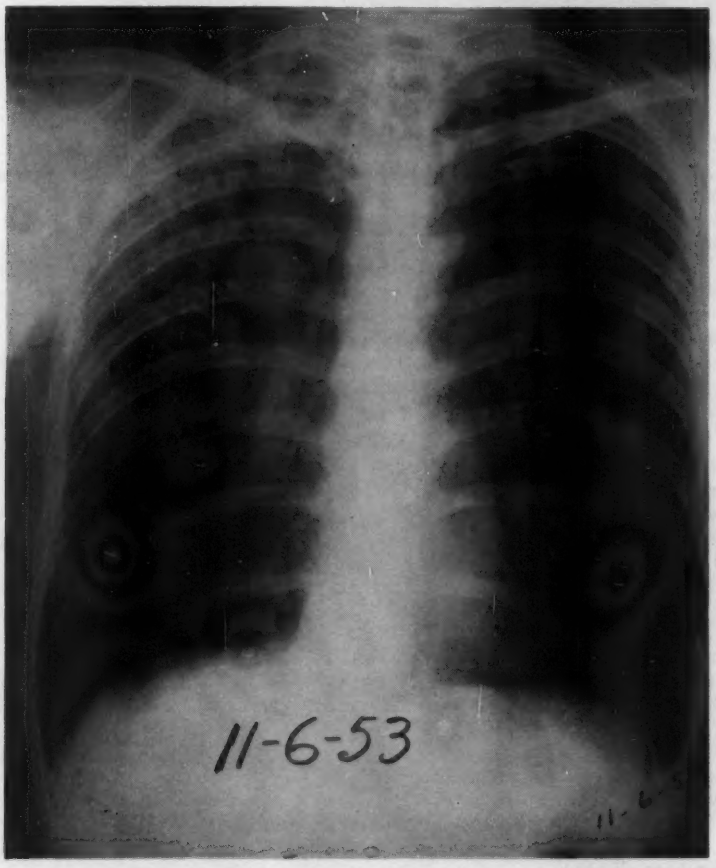

FIG. 2. Spread to entire right upper lobe with apical and subclavicular cavities.

the diagnosis could only be presumptive until confirmed by direct examination of the affected tissue.

Subsequent Progress: On September 2, 1953, the patient reported he felt well except for nervousness because of increased responsibility at work following his promotion to foreman. He did not report again until November 4, at which time he stated that nine days previously he had noted anorexia and marked fatigue, and three days later felt worse and was found to have a temperature of 102° F. The doctor at his place of employment gave him a dose of antibiotic, which made him

feel better, and he had had no fever since, but had noted slight cough and expectoration. He had continued to work, and now had a ravenous appetite and was regaining his strength. He brought with him a chest film taken in the plant the day of his fever, which showed a dense infiltration on the *right* side, involving the greater portion of the upper lobe, with several cavities.

Questioning elicited the fact that about five weeks previously he had donated a pint of blood for a nephew with a gangrenous leg. He had felt tired the next day but had driven all that night up into the High Sierras, where he spent a week hiking and fishing, though still feeling tired and "achy."

Physical examination revealed evidence of pathologic changes in the upper right lung. A film showed dense infiltration involving the entire upper right lobe, with apical and subclavicular cavities (figure 2).

He was sent home to bed. A sputum specimen was sent to the laboratory for examination for *Histoplasma capsulatum*. No organisms were found on direct smear, so culture and guinea pig inoculation were done. Another Mantoux test, PPD .0001 mg., was done, with negative results.

He returned eight days later, at which time his expectoration was somewhat increased. Fluoroscopic examination revealed no material change in the new lesion. As its appearance was somewhat suggestive of a Friedländer's bacillus infection, a sputum specimen was sent to the laboratory to determine whether any new invaders were present. Only the ordinary pyogens were found. He was then put on a mixture of penicillin and streptomycin in daily doses for 10 days to clear any pyogenic infection that might be present.

Two weeks later he reported that he was feeling better. A film showed improvement on the right side, but a 2.5 cm. cavity persisted. His antibiotics were continued for another five days. On December 28 a sputum culture started on November 6 was reported as showing no *H. capsulatum*.

On November 30 a fresh specimen of sputum was examined at the laboratory. No bodies of *H. capsulatum* or other fungi were found in the wet mount, and culture showed no growth of *H. capsulatum* after four weeks.

On January 5, 1954, a sputum culture for tubercle bacilli started on November 9 was reported as negative; animal inoculations for both tubercle bacilli and *H. capsulatum* done at the same time were also reported negative.

On January 7, 1954, he was feeling much better. Fluoroscopic examination and a film showed marked improvement in the infiltration in both lungs, but a cavity was still present on each side (figure 3).

Through the good services of Dr. C. Richard Smith and the California State Board of Health Laboratory at Berkeley, a sample of blood serum was examined by the State Department of Health of Georgia for complement-fixing antibodies and found to be positive for histoplasmosis in a dilution of 1:256.

On January 27 a bronchoscopic examination (by L. A. B.) revealed a normal bronchial tree with a small amount of pus in each side, which was aspirated. After an hour's search the laboratory technician reported the finding of three acid-fast bacilli in the aspirate. Next day another Mantoux test, PPD .0001 mg., was again negative.

The high complement-fixation test for histoplasmosis was confirmatory of that infection, probably in an active form, but did not tell us whether the new lesion was a part of the same infection, though that seemed most likely. While the Mantoux test was persistently negative, it was not possible to rule out entirely a rare type of tuberculous infection. The finding of three acid-fast bacilli after an hour's search was not at all convincing, but we felt it could not be ignored.

After conference the conclusion was reached that only surgical resection of the affected areas offered any expectation of cure.

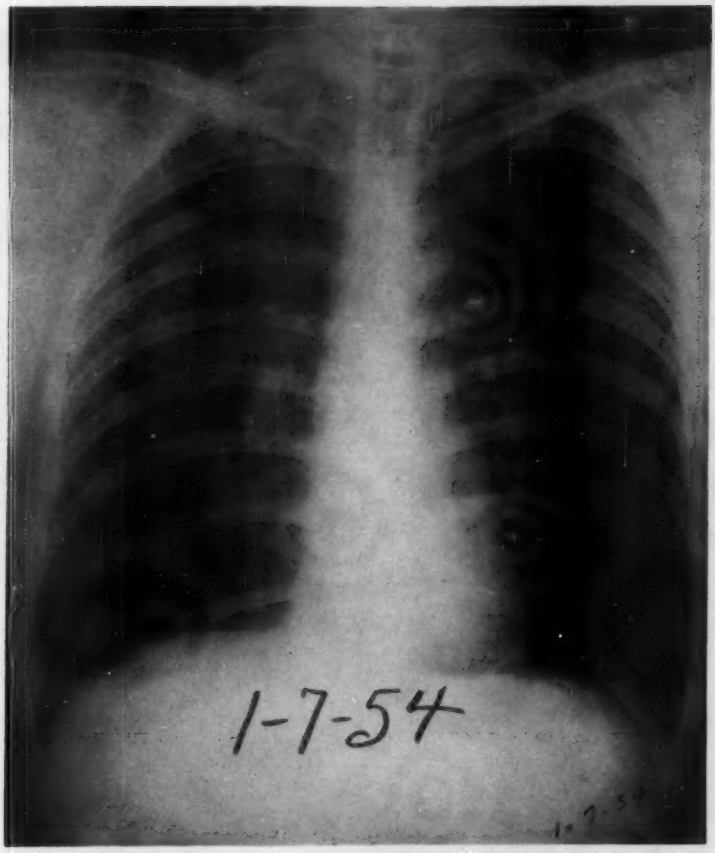

FIG. 3. Recession of apical lesions but persistent cavities on both sides.

For four weeks before surgery the patient received streptomycin, 1 gm. twice weekly, isoniazid, 200 mg. daily, and para-aminosalicylic acid, 12 gm. daily.

Six weeks after the complement fixation test above noted, another test was done at the laboratory of Dr. C. Richard Smith. The findings were practically identical with those of the previous test.

On March 3, 1954, a resection was done (by L. A. B.), with removal of the apical and posterior segments of the right upper lobe. A postoperative film showed an apparent spread of the infection into the lower part of the right upper lobe, with a less intense but fairly wide extension into the upper left lung.

One week after operation the laboratory reported that the tissue removed showed granulomatous change, not distinctive of histoplasmosis or tuberculosis.

On March 19 another complement fixation test for histoplasmosis showed positive only in a dilution of 1:64 and lower, one dilution less than the previous test.

Two weeks postoperatively pneumoperitoneum was induced, and was continued for approximately five months.

On March 24, three weeks after operation, there was beginning growth of the culture from the tissue, and on March 26 *H. capsulatum* was identified. On receipt of this word the antituberculosis drugs were discontinued.

One of us (E. A. R.) had learned of some work being done by the William S. Merrell Company in the chemotherapy of histoplasmosis, and through their good offices we were able to secure a supply of MRD-112 (chemical name). On April 1, 1954, the patient entered La Vina Sanatorium (W. H. O.), where the drug was administered daily.

On May 15 a complement fixation test by Dr. Smith showed further improvement, and on June 3 two and one-half segments of the upper left lobe were resected. Growth of *H. capsulatum* from the resected tissue was accomplished with considerably more difficulty than from the tissue removed at the first operation.

The drug was continued to a total of 90 injections, and the patient was discharged to his home on July 26, seven weeks after the second operation, at which

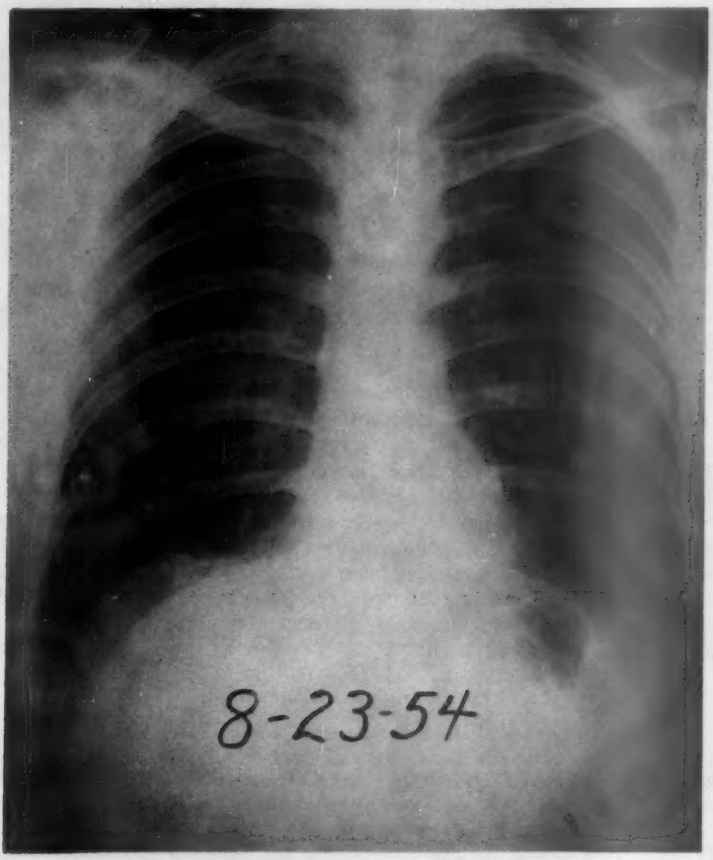

FIG. 4. Clearing of lung fields.

time he was walking up to one and one-half miles daily. A month later the lung fields were practically clear (figure 4). He was feeling well and was reasonably active.

On October 10 complement fixation was positive only in a dilution of 1:16.

Source of Infection: As above noted, the patient denied having at any time been in the endemic areas in the middle portion of this country except for the two days spent in New Orleans in 1945. The studies reported by Furcolow and Grayston [1] indicate that infection is present in many areas not yet identified. Little is known about the prevalence of this infection in other countries, but we are justified in believing that it is probably widespread. A single study, recently reported,[2] of 1,000 individuals in Panama showed a high incidence (38%) of reactors to the test, so the soil of that country is probably fairly heavily infected. As Colombia is immediately adjacent to Panama the same may well be true there. At present the Philippine Islands are not considered to be the site of many infections. The most likely source of his infection, therefore, would be Panama in 1945, with four days' exposure, or (less likely) Colombia, with one year's exposure, with the remote possibility of New Orleans, two days' exposure, being a factor.

The fact that he had an attack of what was probably pleurisy in July, 1949, while in Colombia, suggests that the lesion in the left lung was probably active at that time. A minifilm taken there three months later and recently made available shows in the left apex an apparently acute exudative lesion of approximately the same size as the area of involvement shown on subsequent films, with evidence of general slight pleural thickening. We feel that this film confirms our suspicions.

Summary

A case is reported of progressive pulmonary histoplasmosis closely resembling reinfection-type cavitary tuberculosis, with an acute pneumonic spread and cavity formation in the contralateral lung. Surgical excision of the more recently infected tissue was followed by some dissemination of the process in both lungs, but later excision of the involved tissue in the lung first infected was uncomplicated, and the patient is apparently free of active disease.

The appearance of his film after a short course of antituberculosis medication was suggestive, though not conclusive, that it exerted a deleterious effect on the lesions, as was noted by Prior, Saslow and Cole.[3]

While the results of the administration of the MRD-112 daily for a period of 90 days cannot be said to be conclusive, we feel that it probably had a beneficial effect on the histoplasmosis lesions, as evidenced by the rapid improvement in the disseminated lesions resulting from the first operation, a slight diminution in the size of the cavity in the left apex prior to the second operation, and the much greater difficulty in culturing the organisms in the pulmonary tissue removed at the second operation.

Summario in Interlingua

Histoplasmosis pulmonar—exactemente como coccidioidomycosis pulmonar—pote simular tuberculose si strictemente que le differentiation super le base de examines physic e radiologic deveni impossibile. Relativemente pauco es cognoscite in re le extension geographic de histoplasmosis pulmonar, sed il ha bon rationes pro creder que iste morbo es multo plus extense que lo que on ha suspicite, tanto in le Statos Unite como etiam al extero. Per consequente, le recognition de histoplasmosis pulmonar deveni progressivemente plus importante.

Es reportate un caso de progressive histoplasmosis pulmonar de alte similitude a tuberculose cavitari del typo de re-infection, con acute dissemination pneumonic e formation de cavitate in le pulmone contralateral. Le lesion initial se trovava in le apice del pulmone sinistre. A iste stadio le radiogramma esseva integremente compatibile con un diagnose de tuberculose. Tamen, repetite tests de Mantoux con purificate derivato proteinic in varie doses esseva negative. Tests cutanee a coccidioidina e tests de fixation de complemento seral como etiam tests a precipitina esseva negative. Le examine del sputo revelava nulle bacillos tuberculotic. Lavage gastric esseva negative pro bacillos tuberculotic in culturas in vitro e in inoculationes in porcos de India. Lavage gastric culturate e inoculate pro *Coccidioides immitis* esseva etiam negative.

Un test a histoplasmina esseva positive. *Histoplasma capsulatum* esseva culturate ab un lesion de porco de India post quasi sex menses de incubation.

Un revista de ancian roentgenogrammas monstrava que le lesion habeva essite sub disveloppamento durante un periodo de al minus cinque annos, ben que durante le passate tres annos illo habeva essite practicamente stationari.

Le patiente admitteva nulle symptomas, o local o systemic. Leve accessos de tusse e expectoration esseva attribuite per ille al fumar de tabaco.

Le excision chirurgic in histos de infection recente in le pulmone dextere esseva sequite per un certe grado de dissemination del processo in ambe pulmones. Le excision, tres menses plus tarde, del histos involvite in le pulmone sinistre esseva noncomplicate. Le patiente ha recomenciate laborar e pare esser libere de morbo active.

Nos ha le impression que le administration de MRD-112 [William S. Merrell Company] durante 90 dies post le prime operation exerceva un certe grado de influentia benefic super le lesiones.

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FENESTRATIONS OF THE AORTIC VALVE CUSPS AS A CAUSE OF AORTIC INSUFFICIENCY AND SPONTANEOUS AORTIC VALVE CUSP RUPTURE*

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Introduction

Insufficiency of the aortic valve is caused most frequently by rheumatic fever or syphilis. Occasionally aortic insufficiency may be a result of bacterial endocarditis, dilatation of the aortic valve ring, hypertension and aortic arterio-

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sclerosis, dissecting aortic aneurysm or trauma. No mention is made in the commonly used texts of cardiology, medicine and pathology of fenestrations of the aortic valve cusps as a cause of aortic insufficiency or of spontaneous aortic valve cusp rupture.[1, 2, 3, 4, 5] In fact, the literature on fenestrations of the semilunar valves is quite scant. In 1897, a study of 4,252 autopsies on mentally ill patients revealed 148 cases of congenital abnormalities of the heart.[6] Of these abnormalities, 101 cases were fenestrations of the various valves, of which 84 cases occurred in males. The aortic valve was the most frequently involved. It was felt that fenestrations were of no clinical significance and were of congenital origin. The age of the patients was not considered important. However, in 1929, in a study of 300 successively examined hearts, another author found one or more fenestrations in 82% of the cases, with pulmonary and aortic valve involvement being approximately equal in frequency.[7] This study also demonstrated that the number of fenestrations increased with age, while developmental defects decreased with age. Hence, it was felt that the fenestrations were acquired as a result of the persistent strain of the diastolic pressure on the valves. In two of the hearts the fenestrations were so large that the possibility of aortic insufficiency was suggested, but clinical data were absent in these cases and in most of the others.

In the 59 autopsy-proved cases of traumatic rupture of the aortic valve published up to the present there is no reference to fenestrations as an underlying cause of the rupture.[8, 9, 10, 12] Out of seven cases of nontraumatic rupture of aortic valve cusps with syphilitic aortitis reported by Carroll in 1951, there were two cases with small fenestrations present in the valve cusp above the line of closure of the valve.[11] In one of these two the tear was through the fenestrations. It was suggested that the fenestrations may have made the valve more susceptible to rupture. In 1951, Castleman reported a case of marked fenestration of the aortic cusps leading to aortic regurgitation, cardiac hypertrophy and dilatation.[13] The fenestrations extended below the line of closure of the valve and hence allowed regurgitation. The microscopic sections of the cusps revealed extensive mucinous degeneration, which is similar to that in the aorta itself in older persons and was felt by this author to be related to *medionecrosis aortica cystica.*

In the following case, fenestrations of the aortic semilunar valves caused aortic insufficiency and eventual aortic valve cusp rupture.

Case Report

A 67 year old Negro male was first admitted to the Seattle Veterans Administration Hospital on July 22, 1954. He had been in good health until about one month prior to admission, when he gradually developed dyspnea on exertion. This became more severe over a two to three week period; orthopnea and paroxysmal nocturnal dyspnea appeared about the same time, as did a nonproductive cough. On admission he could walk about one block without resting and could climb about 15 steps. No history of previous cardiac difficulties was elicited. He gave a vague history of one bout of nonmigratory rheumatism lasting several weeks at age 19. Two to three years prior to admission he had been told that his blood pressure was moderately elevated. He also had suffered a slight stroke, with resultant minimal left hemiparesis, two years prior to admission.

Physical examination revealed an alert, obese Negro male who was moderately

dyspneic on exertion or in the supine position. Blood pressure was 168/78 mm. of Hg. The pupils were round and equal, and reacted to both light and accommodation. Except for arteriolar narrowing, the funduscopic examination was negative. The thorax was barrel-shaped. There were a few crackling râles at the right lung base. The left cardiac border was percussed 3 cm. beyond the midclavicular line in the left fifth intercostal space. There was a normal sinus rhythm with a rate of 88 per minute. A grade III soft variable systolic murmur was present at the apex, and an early, prolonged, decrescendo diastolic murmur was noted over the precordium maximal at Erb's area; a short rumble at the end of diastole at the apex was suggestive of an Austin Flint murmur. The first heart sound at the apex was not accentuated. Heart sound recordings did not confirm a presystolic apical component to the murmurs.

There was a Corrigan pulse at the radial artery, and Duroziez' sign was present over the femoral artery. There was no edema, cyanosis or clubbing. The remainder of the examination was within normal limits except for an obese abdomen, a 2 plus enlarged prostate, and a residual left hemiparesis.

The laboratory and x-ray findings were as follows: hematocrit, 40%; white blood cell count, 6,300/mm^3; sedimentation rate, 12 mm. per hour (corrected). The urinalysis was unremarkable except for 40 mg.% of protein. The serologic test (VDRL) was negative. Spinal fluid examination revealed no cells, 40 mg.% of protein, and negative serologic test for syphilis. The total serum cholesterol was 250 mg.%.

The chest x-ray film revealed considerable left ventricular hypertrophy. The lung fields were clear. Fluoroscopy revealed the lungs, diaphragm and pulmonary markings to be normal; there was a 2 to 3 plus left ventricular enlargement without other chamber enlargement. There was no enlargement of the aorta or visible calcification in the aorta or valves. The esophagus was not displaced.

An electrocardiogram showed a normal sinus rhythm, first degree A-V block (PR interval, 0.24 sec.), and changes compatible with left heart strain and/or myocardial ischemia. The venous pressure was 200 mm. of normal saline (using 10 cm. above the mattress as the zero reference point), and the circulation time was 47 seconds from arm to tongue with Decholin.

The hospital course lasted 45 days. The patient was digitalized and placed on a low-salt, low-calorie diet. He responded well, with disappearance of orthopnea and weight loss of 7 kg. Syphilis was felt to be a possible cause of the aortic insufficiency, in spite of the negative serology, and the patient was therefore given 12,000,000 units of penicillin over a 10 day period. He was discharged September 6, 1954 on digitoxin, 0.1 mg. daily, and a 1000-calorie, low-salt diet.

He was re-admitted on September 10, 1954 complaining of progressively severe dyspnea on exertion, orthopnea, paroxysmal nocturnal dyspnea and ankle edema, though he claimed to have taken digitoxin and to have adhered to the low-salt diet as directed.

Physical examination revealed the temperature to be 98.6° F., the pulse to be regular and 84 per minute, and the blood pressure to be 200/70 mm. of Hg. The patient was dyspneic. There were moist râles at each lung base. The point of maximal impulse of the heart was at the left anterior axillary line in the sixth intercostal space. There was a grade IV, blowing, aortic diastolic murmur, heard throughout the precordium but best at the third intercostal space just to the left of the sternum. A grade III apical systolic murmur was also present. A nontender liver edge was palpable 2 cm. below the right costal margin at the midclavicular line. There was 1 to 2 plus pitting edema of the legs and feet. Corrigan's pulse and Duroziez' sign were present as before. The examination was otherwise unchanged from the initial one.

Serology (VDRL) was persistently negative. The hematocrit was 40%, the white blood cell count 7,200/mm³ and the sedimentation rate 17 mm. per hour (corrected). Urinalysis again was normal except for 40 mg.% of protein. The serum electrolytes were within normal limits. The blood urea nitrogen was 49 mg.%; however, a creatinine determination done on November 1 was 1.7 mg.%. Multiple blood cultures were repeatedly negative. The serum electrolytes were still normal on September 24. The hematologic examination remained normal. Urinalyses continued to show minimal proteinuria.

An x-ray film of the chest on September 19 revealed little change from the previous film except for the development of a small pleural effusion at the left base.

Thirteen electrocardiograms were taken during the last admission. A tracing taken four days after admission revealed probable auricular fibrillation and sagging ST segments in Leads V-5 and V-6, compatible with coronary insufficiency or left heart strain. Subsequent tracings revealed very marked changes in rhythm, ranging from complete heart block with a nodal pacemaker and multifocal ventricular extrasystoles, to normal sinus rhythm with second degree AV heart block, Wenckebach phenomenon, and ventricular escapes. Tracings taken from September 22 through September 27 were compatible with digitalis toxicity. Tracing on December 10, 1954, revealed second degree AV heart block, Wenckebach phenomenon, left heart strain, and/or chronic coronary insufficiency.

The venous pressure was 200 mm. of normal saline; circulation time was 35 seconds from the arm to the tongue using Decholin.

Treatment consisted of digitoxin, diuretics and a low-salt diet as before.

Between September 16 and 17, a striking change developed in the cardiac auscultatory findings. There suddenly developed an extremely loud, grade VI diastolic murmur of a high pitched, whirring quality, loudest in the aortic area, transmitted throughout the precordium and neck, and accompanied by a palpable diastolic thrill in the aortic area. The murmur could be heard without a stethoscope and was superimposed on the diastolic murmur previously noted. The timing of the murmur was confirmed by simultaneous auscultation and fluoroscopy.

The hospital course lasted 117 days. Peripheral edema and the moist râles at the lung bases were persistently present. Cheyne-Stokes respiration, clouded sensorium and bouts of syncope were noted. Although multiple blood cultures were negative, a three-week course of penicillin in a dose of 600,000 units intramuscularly every three hours, and streptomycin, 0.5 gm. intramuscularly every eight hours, was given because of the possibility of subacute bacterial endocarditis. The new murmur continued unchanged in spite of the medication.

Digitalis intoxication became a problem at least twice and was treated with lower doses of digitoxin, or withdrawal of the drug and potassium administration.

The patient continued to be periodically irrational and incontinent and to have episodes of Cheyne-Stokes respiration. On November 4 the circulation time was 37 seconds, arm-to-tongue with Decholin, and the venous pressure 180 mm. of normal saline. A productive cough and basal râles became more pronounced. On November 26 syncope occurred, raising the question of Adams-Stokes attacks. On December 4 a right femoral arterial tracing showed a normal ejection time, lack of a dicrotic notch, and pressures of 184 to 200 mm. Hg systolic and 40 to 48 mm. Hg diastolic. On January 3, 1955, the patient began having more prolonged periods of Cheyne-Stokes respiration and confusion. The next day he had prolonged apnea, from which he recovered, but shortly thereafter he was found dead.

The final clinical diagnoses were as follows: (1) arteriosclerotic and possibly luetic heart disease with left ventricular hypertrophy, probable luetic aortic valvulitis, aortic insufficiency, aortic valve cusp rupture or cusp eversion, and congestive heart

failure, class IV E; (2) right cerebral vascular accident with residual left hemiparesis, (3) exogenous obesity, moderate.

Autopsy Findings: The autopsy was done four hours post mortem. The body was that of a middle-aged Negro male measuring 63½ inches in length and weighing approximately 150 pounds. The main findings were limited to the heart and the lungs.

The heart weighed 530 gm. The left ventricular wall measured 2.2 cm. in thickness, the right, 0.7 cm. The tricuspid valve and the pulmonary valve rings measured 13.5 cm. and 8.5 cm. in circumference, respectively, and the cusps were thin and pliable. There was a small fenestration in the lunate portion of the anterior and right pulmonary valve cusps near their common commissure, and in the left and right pulmonary valve cusps near the corresponding site, all of which measured 1 to 3 mm. in diameter (figure 1).

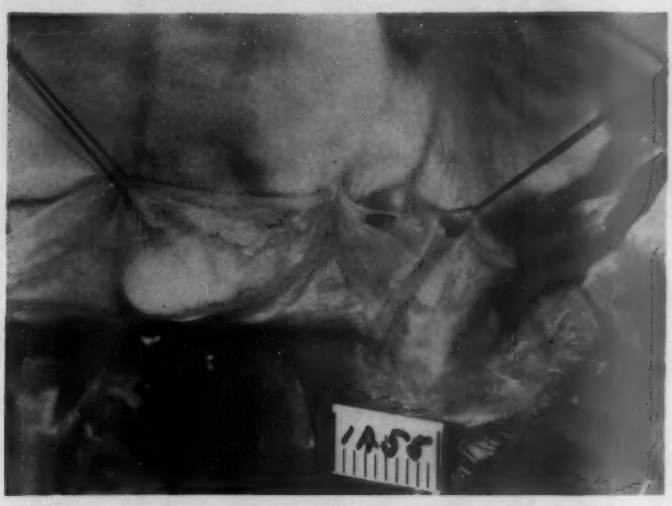

FIG. 1. Gross appearance of the pulmonic valves showing the thinness of the valves and the fenestrations of the valve cusps.

The aortic valve ring measured 8.0 cm. in circumference; the leaflets were thickened and contained several yellow, hard plaques near their junction with the intima of the aorta (figure 2). There was a fenestration measuring 0.4 by 1.1 cm. in both the posterior and right anterior cusps of the aortic valve near their common commissure. These fenestrations extended down into the body of the cusps below the line of valve closure. The right anterior cusp had ruptured near its attachment to the aortic intima, leaving the upper border of the fenestration open (figure 3). There were thin strands of tissue, separated by small fenestrations, lateral to the main fenestration in the right anterior cusp. These strands ran in a vertical direction from the free margin to become attached to the aortic intima. These two cusps were fused together and moderately thickened at their commissure, where there were several plaques (figures 2 and 3). The lunate portion of the posterior cusp near its aortic intimal attachment was markedly thinned. There were also some thickening and fusion of the posterior and left anterior cusps at their common commissure. There was a small fenestration measuring 1 to 3 mm. in diameter in the

FIG. 2. Gross appearance of aortic valve showing fenestrations, rupture of the valve cusp through a fenestration, fusion of the commissures of the valve, and the gross appearance of the aorta.

lunate portion of both the left anterior and the right anterior aortic cusps near their common commissure.

The sinuses of Valsalva were abnormally large and roomy. The ascending aorta was slightly enlarged in a fusiform manner, and a moderate degree of athero-

FIG. 3. A closer view of the fenestrations of the aortic valve and of the ruptured aortic valve cusp.

FIG. 4. Photomicrograph of an aortic valve cusp showing evidence of mucoid degeneration.

sclerosis was present throughout the aorta. No evidence of syphilitic aortitis was seen grossly.

The mitral valve ring measured 12.0 cm. in circumference and its cusps were slightly thickened. The chordae tendineae were thickened and had a whitish discoloration. The tips of the columnae carneae were whitish yellow in color.

Within the right auricular appendage, a 4 by 2 cm. antemortem grayish white to pink thrombus adhered tenaciously to the endocardium. The endocardium of the outflow tract of the left ventricle was thickened and white and contained several hard, yellow plaques. There were no diastolic pockets.

Sections through the interventricular septum revealed no abnormalities.

The coronary ostia were widely patent and were in normal position. The coronary arteries showed a moderate degree of atherosclerotic plaquing; however, the lumina were not completely occluded at any point.

In the lower lobe of the right lung there was a large, wedge-shaped hemorrhagic infarct. The corresponding branch of the right pulmonary artery contained a large, antemortem, grayish pink blood thrombus. Similar but much smaller areas were present in the apex of the right upper lobe and the superior segment of the left lower lobe. In the branches of the pulmonary arteries leading to these areas there were antemortem thrombi.

In general, the microscopy confirmed the gross findings. Sections taken from various portions of the aortic valve and stained with hematoxylin-eosin revealed the thickening and scarring to be composed of a rather acellular, amphoteric, collagenous connective tissue (figure 4). In the ground substance there was fine vacuolation which appeared with periodic acid Schiff stain to be due to empty tissue interspaces. The connective tissue stained quite deeply with the periodic acid Schiff stain. In some of the sections foci of calcification and fat droplets, demonstrated with oil red 0, were present at the base of the valve. There was no active inflammation.

Similar sections and stains of the mitral valve revealed thickening and vacuolation of the leaflets with connective tissue which had a marked affinity for the periodic acid Schiff stain. The endothelium was intact, and there was no active inflammation or calcification.

The myofibers of the left ventricle were enlarged with large blue nuclei; there was no evidence of hemorrhage or inflammation. One of the sections included a coronary artery which showed marked intimal thickening and hyalinization, with only a slitlike lumen remaining. The pericardium was unremarkable.

Sections through the ascending aorta revealed a classic picture of atherosclerosis. There were a few chronic inflammatory cells in the adventitia, but no endarteritis of the vasa vasorum was present and the media was well preserved. In the sinus of Valsalva the wall was markedly thickened with collagenous tissue.

The important anatomic diagnoses were as follows: (1) fenestrations of the aortic valve cusps leading to (a) aortic valve insufficiency, (b) rupture of an aortic valve cusp, and (c) left and right ventricular hypertrophy; (2) rheumatic aortic and mitral valvulitis, old, inactive; (3) mucinous degeneration of the aortic and pulmonic valves, of unknown etiology; (4) right auricular thrombosis with multiple pulmonary emboli and infarctions; (5) coronary atherosclerosis, moderate to severe; (6) acute and chronic passive congestion of the lungs and liver; and (7) pulmonary artery atherosclerosis and interstitial pulmonary fibrosis.

Discussion

It is difficult to be sure of the exact etiology of the fenestrations in this case. Perhaps a combination of factors was responsible. The following multiple factor theory is presented as being a logical explanation of the valvular pathology.

The suggestion of rheumatic fever in the history, the thickening of both the aortic and mitral valves, and the fusion of the aortic valve cusps make old rheumatic valvular disease likely.

It is known that normally the lunate portions of the semilunar valve cusps come together without friction when the valve closes. The fusion of the commissures in this patient, occurring many years before, may have caused a portion of the body of the cusps to have been brought together with abnormal friction and force for a prolonged period of time. In combination with mucoid degeneration of the valve cusps, the abnormal friction during valve closure may well have produced thinning and then gradually enlarging fenestrations of the semilunar valves. However, the case of Castleman [13] showed no evidence of rheumatic valvulitis. It is possible that the stress of prolonged valve closure acting on the degenerated valves may explain the appearance of fenestrations without other associated pathology.

In this case, congenital fenestrations of the aortic valve are felt to have played little if any part in the pathogenesis of this disease.

The rupture of the valve cusp can be easily explained by considering the repeated stress placed on the remaining strand of already weakened valve tissue.

Apparently the fenestrations allowed sufficient reflux of blood to cause left ventricular hypertrophy and dilatation and, finally, congestive heart failure when the heart could no longer compensate. The rupture of the right anterior aortic valve cusp no doubt accounted for the sudden appearance of the new murmur and the rapid increase in the degree of congestive failure.

Although rare, fenestrations of the aortic valve should be considered in the differential diagnosis of all cases of aortic insufficiency, especially if the evidence for the more common causes of aortic insufficiency, such as syphilitic valvulitis and rheumatic valvulitis, is lacking or equivocal. In addition, fenestrations should be considered as a predisposing factor to rupture of an aortic valve cusp.

Summary

A patient in whom fenestrations of the aortic valve caused clinical aortic insufficiency, congestive heart failure and aortic valve cusp rupture has been described in some detail.

It was postulated that the fenestrations were caused by friction acting on the degenerated valves; the role of rheumatic valvulitis was also discussed.

Fenestrations of the aortic valve should be considered as a possible cause of unexplained aortic insufficiency and as an etiologic factor in the rupture of an aortic valve cusp.

Acknowledgments

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Mr. Paul Newman was the medical photographer.

Summario in Interlingua

Ben que fenestrationes del valvula aortic ha essite notate non infrequentemente in series autoptic, le correlation inter tal fenestrationes e symptomatic morbo aortovalvular ha attirate pauc attention.

Es reportate le caso de un negro mascule de 67 annos, con dyspnea, orthopnea,

edema talari, e altere symptomas de congestive disfallimento cardiac. Le examine physic revelava roncos humide in le base pulmonar e edema pedal. Le corde esseva allargate verso le basso e le sinistra. Esseva notate un dulce murmure systolic apical e un sufflante murmure diastolic de alte intensitate. Iste ultime esseva melio audibile in le area aortic e al margine sinistro-sternal del quarte interspatio. Le signo de Duroziez esseva positive. Le pression del sanguine esseva 200/70 mm Hg. Durante le hospitalisation del patiente, un multo intense e sifflante murmure diastolic appareva subitaneemente in le area aortic. Post un prolongate curso de intractabile disfallimento congestive, le patiente moriva.

Le autopsia monstrava multiple fenestrationes del valvulas aortic e pulmonic. Le cuspide dextero-anterior del valvula aortic esseva rupturate a transverso le area de un fenestration. Esseva etiam notate le fusion del commissuras del valvula aortic, lo que pareva indicar un ancian valvulitis rheumatic. Sectiones del cuspide del valvula aortic revelava un degeneration mucinoide del substantia valvular.

Nos arrivava al conclusion que le fusion del commissuras causava un friction anormal del valvulas. Nos opinava que le fenestrationes esseva effectuate per le friction repetitive in le degenerate valvulas.

Fenestrationes del valvulas semilunar deberea esser prendite in consideration in le etiologia de insufficientia aortic (o pulmonic) o de ruptura de cuspide aorto-valvular, quandocunque le plus commun causas de iste lesiones non pare probabile.

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BUCKLING OF THE CAROTID ARTERY DEMONSTRATED BY ANGIOCARDIOGRAPHY *

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THE demonstration by angiocardiography of buckling of the right common carotid artery has not previously been reported. The purpose of this article is to document such a case, in which the patient presented with a painful, pulsatile mass at the root of the right neck where the differential diagnosis from aneurysm could not be clinically ascertained. Opacification of this vessel by contrast medium provided indisputable proof of common carotid buckling, and the patient was spared an exploratory operation.

Buckling of the common carotid carotid artery had been studied in detail prior to the development of angiocardiography. Parkinson et al.[1] studied clinically, at operation and at autopsy, the findings in 47 cases of right common carotid kinking. A detailed description of the clinical and pathologic features in these cases is given.

Following the introduction of angiocardiography by Robb and Steinberg [2] most great vessel abnormalities were explored. In particular, buckling of the innominate artery has received intensive angiographic study. Honig et al.[3] have recently reported 12 cases of innominate artery buckling which produced a right paratracheal shadow on the posterior-anterior chest roentgenogram.

Though superficially similar, buckling of the innominate and buckling of the carotid produce two entirely different clinical pictures. In the first case there is a rounded density in the right paratracheal region, and the differential diagnosis from tumor, aneurysm, infiltration or enlarged nodes must be made. In the latter case the patient presents with a normal chest roentgenogram, complaining of a pulsatile mass in the right lower neck. The problem here is to determine whether this is an extravascular mass transmitting pulsation, or a vascular abnormality such as aneurysm or kinking. It is interesting to note that in Honig's series of innominate bucklings, four cases are described in which "palpable and visible pulsations at the base of the right side of the neck were present." They do not so specify, but it appears obvious from the illustrations in their article that this pulsation might have been due to associated tortuosity of the common carotid artery, and not primarily to the innominate buckling, as they have assumed.

True kinking of the carotid is quite different from simple tortuosity because it is usually characterized clinically by the appearance of a big, distinct, pulsatile mass (about the size of a chicken's egg), as opposed to simple pulsations.

CASE REPORT

A 72 year old Puerto Rican female was admitted to Bellevue complaining of "pain in the neck." The patient had noted the presence of a pulsatile mass at the root of the right neck for about two years. The pulsations were aggravated by

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tachycardia and any form of physical exertion. The patient also complained of shortness of breath on exertion, swelling of both ankles during the day, two-pillow orthopnea, and a paroxysmal nocturnal "choking sensation."

Physical examination revealed a well nourished white female with a blood pressure of 160/80 mm. of Hg and pulse of 92. In the right neck, directly under the middle of the sternomastoid muscle and extending down to the clavicle, a distinct mass was palpable which was slightly tender to deep pressure. The mass was 4 by 9 cm., with its long axis placed vertically. Grasping the mass between two fingers the examiner could feel a distinct, expansile-type pulsation (figure 3).

Chest roentgenogram showed widening and tortuosity of the supracardiac aorta, with a calcific plaque in the aortic knob. The heart was slightly enlarged in the transverse diameter, with downward and outward displacement of the apex.

Laboratory examination disclosed these values: Fasting blood sugar, 100 mg./100 c.c.; nonprotein nitrogen, 21 mg./100 c.c.; blood cholesterol, 330 mg./100 c.c. The Mazzini test was negative. Urinalysis was normal. Red blood count was 5,880,000 cells/cu. mm.; hemoglobin (Sahli), 17 gm.; white blood count, 8,800 cells/cu. mm.; erythrocyte sedimentation rate, 17 mm. in one hour. The differential count was 61 polymorphonuclear leukocytes, 38 lymphocytes and 1 eosinophil.

Angiocardiography was performed in the left oblique position following the rapid injection of 70% Urokon into the right antecubital vein. Films were taken at 3½, 5½, 7½ and 9 seconds.

The film at 7½ seconds showed a clear-cut outline of the aortic arch and its major branches. The innominate artery was rigid and straight, bifurcating at a high level into the right subclavian and right carotid arteries (figure 1). The subclavian

FIG. 1. Angiocardiogram at 7½ seconds following injection. The arch of the aorta and its major branches are opacified by dye. (Illustration is superior to the original x-ray film because of photographic "dodging" used in making print.)

FIG. 2. Tracing of figure 1. Numbers: 1, arch of the aorta; 2, innominate artery; 3, right carotid artery; 4, origin of right subclavian from medial wall of the innominate; 5, right subclavian; 6, left subclavian; 7, left carotid; 8, clavicle. Note the marked kinking of the right carotid. There is moderate tortuosity of the left subclavian and left carotid.

took its origin from the medial wall of the innominate and circled around posterior to it to emerge laterally, while the carotid continued into the neck, making a sharp, crooked, reverse-S turn in the neck. It was this buckling which was responsible for the mass in the neck. The left subclavian and left carotid arteries also showed a moderate degree of tortuosity.

COMMENT

This case presents features of both clinical and radiologic interest. First, it demonstrates the fallacy of certain widely held clinical signs. Expansile pulsation is regarded by some clinicians [4] as pathognomonic of aneurysm when seen or felt. Our case presented this type of pulsation. The mechanism whereby expansile pulsation can be simulated by kinking is seen by reference to the inset in figure 3. At systole, the right carotid will fill with blood and tend to straighten out, thereby producing a lateral motion or thrust which simulates expansile pulsation.

Second, its occurrence in an elderly, hypertensive, arteriosclerotic female is almost, in itself, diagnostic. Hypertension occurred in 75% of Parkinson's 47 cases, and all his cases were female. Only one case in a male is reported in the literature.[5] According to Parkinson, "A pulsating tumour in the right side of the neck in a patient over the age of 40 . . . should be considered a kinked carotid unless it is accompanied by signs and symptoms of pressure on adjacent structures, and by radiological or other evidence of involvement of the innominate and aorta."

Third, the origin of the kinked carotid is of interest. Honig has expanded Parkinson's theory for the mechanism of innominate buckling: "Hypertension produces unfolding and dilatation of the aorta, and arteriosclerosis which usually coexists, produces concomitant lengthening. The aortic arch thereby becomes elevated, and tortuosity of the innominate, and secondarily of the right carotid and right subclavian result. On the left, the subclavian and carotid arteries are free, and the tortuosity is distributed over the length of the vessels without appreciable kinking. On the right side, the subclavian tends to anchor the innominate at its bifurcation, resulting in buckling when elevation occurs."

FIG. 3. Representation of the location of the tumor mass in the neck. The inset demonstrates how a kinked carotid can produce simulated expansile pulsations.

In our case the elevation of the aortic arch secondary to hypertension and arteriosclerosis is reflected in the moderate tortuosity of the left subclavian and left carotid arteries. The innominate, however, remained rigid and straight, and rose with the elevation of the arch. The subclavian failed to anchor the innominate at its bifurcation, and consequently a high bifurcation took place. Since the division of carotid into internal and external branches was itself

anchored, the common carotid, being caught between two ends which were gradually getting closer, was compelled to buckle.

Summary

A case of right common carotid buckling demonstrated by angiocardiography is presented. This is believed to be the first case so reported in the literature. The etiologic, clinical and radiologic features are discussed.

Summario in Interlingua

Isto representa le prime caso reportate in que excurvation del arteria carotide dexterocommun es demonstrate angiocardiographicamente durante le vita del patiente. Le aspectos clinic del caso esseva typic pro le syndrome del carotide excurvate e justificava un forte suspicion de ille diagnose. Le presentia de un typo expansional de massa pulsante al dextera basse del collo de un feminina de plus que 40 annos de etate (con concomitante signos clinic o roentgenographic de arteriosclerosis e hypertension) es quasi pathognomonic. Le pulsation de typo expansional simula aneurysma sed resulta, de facto, ab un pulsata sufferite per le pariete del vaso excurvate durante le systole. Le etiologia de iste condition es a trovar in hypertension e arteriosclerosis. Iste duo processos pathologic resulta in un allongation e elevation del arco aortic que, de su parte, produce un elevation del arteria innominate in le region de su bifurcation in arteria subclavian e commun arteria carotide. Ben que assi le portion initial del arteria carotide es forciate a elevar se, su extremitate distal remane fixe, e in tanto que le duo areas se approcha le un verso le altere, le vaso debe excurvar se.

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PROGRESSIVE BACTERIAL SYNERGISTIC GANGRENE: REPORT OF A CASE TREATED WITH CHLORAMPHENICOL *

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History

A case of clinically recognizable progressive bacterial synergistic gangrene was reported as early as 1909.[1] Two other cases were reported in 1924,[2, 3] but

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it was not until 1926 that Meleney clearly demonstrated the etiology of the infection.

Etiology

Bacteriologic studies [4] were made by Meleney on the lesion of a patient who had developed a progressive gangrene of the abdominal wall following the surgical drainage of an appendiceal abscess. A micro-aerophilic nonhemolytic streptococcus was cultured from far out in the spreading periphery of the lesion. *Micrococcus pyogenes* var. *aureus* (hemolytic *Staphylococcus aureus*) and diphtheroid bacilli were cultured from the gangrenous margin. The synergistic action essential to produce the gangrene was demonstrated by animal inoculation studies.

Cultures of the micro-aerophilic nonhemolytic streptococcus were injected subcutaneously into guinea pigs and rabbits, producing a slight redness and swelling on the day after injection. This rapidly subsided without any evidence of gangrene. Cultures of the *M. aureus* were injected and produced red, tender swellings, and in three of nine animals a superficial gangrene. However, the combination of micrococci and streptococci injected into rabbits and guinea pigs rapidly produced large, red, tender swellings which subsequently became gangrenous and were much more extensive than those produced by injections of micrococci alone.

The diphtheroid bacilli alone and in combination with the streptococci and micrococci did not produce gangrene.

Meleney confirmed this synergistic relationship in experiments carried out with organisms isolated from a second patient with the disease reported in 1931,[5] and named the entity progressive bacterial synergistic gangrene.[6]

Since then more than 100 cases have been reported.[7] In two reported cases [8] an organism other than *M. aureus* in combination with micro-aerophilic nonhemolytic streptococci has been proved with animal inoculation studies to have caused the disease. *Proteus vulgaris* and streptococci were isolated from one patient, and *M. albus* and streptococci from the second.

M. aureus was cultured from the second case later in the course of the disease. This organism also, in combination with the streptococci isolated from the patient, produced lesions in guinea pigs. This was thus the first report indicating that the micro-aerophilic nonhemolytic streptococcus in combination with an organism other than a hemolytic *M. aureus* could produce the disease.

Clinical Appearance

Progressive bacterial synergistic gangrene usually has begun postoperatively in the skin around retention sutures following the drainage of a peritoneal abscess or empyema, although it may also occur around a colostomy, ileostomy, after a trivial superficial accidental wound, or in a skin lesion of long standing. Pain and tenderness of the lesion are nearly invariably present; however, fever, anemia and prostration do not usually occur. Although the lesion has a characteristic appearance, other chronic gangrenous processes—pyoderma gangrenosum (gangrenous impetigo),[9] fusospirochetal infection and amebiasis cutis [10]—must be considered, as well as cutaneous leishmaniasis, cutaneous diphtheria, blastomycosis, bromoderma, and tuberculosis verrucosa cutis.[11] Centrally there

is an ulcer which is granulating and of shaggy consistency. Later the ulcer may be bright red and clean. As the destruction of the dermis is not always complete, islands of epithelium may regenerate from hair follicles and sweat glands.

At the periphery of the ulcer there may be slight undermining. A 1 to 4 cm. wide rim of gangrenous skin surrounding the ulcer is grayish brown, resembling suede leather. This merges with an elevated purplish zone peripherally. The purplish zone, in turn, coalesces peripherally with a 1 to 10 cm. area of erythema which fades into normal skin.

Treatment

The treatment of progressive bacterial synergistic gangrene has not been satisfactory. Surgical extirpation of the affected area and local antiseptics were the earliest therapy used.[4] Penicillin was found to be effective in some cases, but in the presence of penicillinase-producing organisms [12] it was of little value. Parenteral bacitracin has been advocated as the therapy of choice; [7] however, a case has recently been reported which did not respond to bacitracin.[13] Meleney [14] has stated that zinc peroxide with surgery should be used if penicillin and bacitracin are ineffective. Chloramphenicol has been reported to cure one case that was clinically typical but was not bacteriologically confirmed.[15]

The purpose of this communication is to present a bacteriologically confirmed case of progressive bacterial synergistic gangrene produced by micro-aerophilic nonhemolytic streptococcus and *Aerobacter aerogenes* that was treated successfully with chloramphenicol without use of surgery.

Case Report

History: A 32 year old white female housewife was admitted to Duke Hospital on June 16, 1954. Two weeks prior to admission, following a slight trauma, a papular lesion developed on the right lower leg. There was rapid progression to a vesicular and later to a larger bluish, bullous lesion. For 11 days prior to admission the patient had been treated with oral cortisone, 100 mg. per day, penicillin, oxytetracycline and various topical medications, with progressive enlargement of the lesion. She was febrile the week prior to admission but had no systemic symptoms.

Her past history was significant in that during the twenty-second week of her only pregnancy, in 1950, a cellulitis developed in her left axilla. This spread to involve the left anterior chest wall and the posterior axillary region. She was admitted to St. Frances Cabrini Hospital in Alexandria, Louisiana, on the service of Dr. Rodney G. Masterson.* There she was found to have a pneumococcal septicemia and lobar pneumonia. Pneumococci were also cultured from the axillary lesion. Spontaneous miscarriage occurred one week after admission. Treatment was by incision and drainage of the axillary lesion, with bacitracin irrigation of drainage tubes placed in the area. Intramuscular penicillin and streptomycin with intravenous penicillin, chlortetracycline and oxytetracycline controlled the infection, and after a 38 day hospitalization she was discharged cured.

In early 1953 she developed a furuncle on the left knee, which subsided rapidly under penicillin therapy. The remainder of the review of systems was noncontributory.

Physical Examination: Temperature, 39.4° C.; pulse, 132; blood pressure, 144/78 mm. of Hg; respiration, 24. General physical examination revealed no abnormalities.

* Dr. R. G. Masterson kindly supplied the details of this illness.

There was a 10 by 16 cm. purulent, necrotic, ulcerated, tender lesion involving the anterior tibial area of the right lower leg (figure 1). The ulcerated area was encircled by loose redundant skin which was attached peripherally to an edematous, well demarcated, purplish zone. This zone was surrounded by erythema. There was moderate right inguinal adenopathy. Despite the infection and fever, the patient presented surprisingly little evidence of toxicity.

Laboratory Studies: On admission the hemoglobin was 13.2 gm.; leukocyte count, 31,000, with 77 polymorphonuclears, 6 stabs, 1 eosinophil, 12 small lymphocytes and

FIG. 1. Leg lesion on day of admission.

four monocytes. Urine was normal except for a 2 plus reaction for protein. The old tuberculin skin test in a dilution of 1:100 was negative. Histoplasmin, coccidioidin, and staphylococcus toxoid 1:100 intradermal skin tests were negative. The Schick test was markedly positive with a slough. Total proteins were 5.2 gm.%, with 3.6 gm. of albumin and 1.6 gm. of globulin. Electrophoretic studies revealed the albumin and globulin fractions to be present in normal amounts, including gamma globulin. A biopsy revealed pseudoepitheliomatous hyperplasia. Repeated cultures from the leg lesion were negative until June 28, 1954, when *Aerobacter aerogenes* was cultured. On July 5, 1954, a micro-aerophilic nonhemolytic streptococcus was

grown in anaerobic culture. X-rays of the chest, sinuses, gall-bladder, right leg and intravenous urograms did not reveal any significant abnormalities.

Course: The patient was first treated with penicillin and streptomycin, but there was no response and these drugs were discontinued after four days. Locally 1:500 Prophyllin and ¼% acetic acid compresses were employed.

Sulfisoxazole, 4 gm. per day, was then given for three days, without response. For the next six days compresses and 1% gentian violet in 10% alcohol locally were used.

FIG. 2. Leg lesion during first week of chloramphenicol therapy. (Note exposed tibial periosteum.)

On July 1, 1954, despite the lack of a definitive diagnosis, the administration of chloramphenicol, 500 mg. four times daily, was initiated. The patient also received 500 ml. of fresh whole blood intravenously.

The beneficial effect was obvious, and within three days the patient's fever had declined from the previous range of 38° C. to 39° C. to below 38° C. (figure 2). Further evidence of the drug's influence was demonstrated by the patient's exacerbation two weeks after the initial administration of chloramphenicol, when the drug was discontinued for a day and a half. Re-administration of the drug was followed

by improvement. A total of 66.5 gm. of chloramphenicol was given over a 35 day period. Local measures included ¼% silver nitrate and ½% chloramine-T compresses to control the secondary invaders, *Pseudomonas aeruginosa, Escherichia coli* and *P. vulgaris.*

At the time of the patient's discharge on September 4, 1954, the eightieth hospital day, the lesion which at one time had involved nearly the entire lower leg was 2 by 2 cm. in diameter (figure 3). In a communication from the patient on October 19, 1954, she stated that the lesion was completely healed.

FIG. 3. Lesion on day prior to discharge.

Bacteriologic Studies: On July 5 a micro-aerophilic nonhemolytic streptococcus was first grown from anaerobic cultures. On repeated earlier aerobic cultures *Aerobacter aerogenes* was grown; *M. aureus,* however, was never cultured from the lesion.

Individual cultures of *A. aerogenes* and streptococci and mixtures of both were injected subcutaneously into three mice and intradermally into three guinea pigs. The *A. aerogenes* cultures injected subcutaneously alone in a mouse resulted in a 5 mm. nodular abscess in one week which did not break down. The streptococcus cultures injected alone produced no lesion, but the injection of a combination of the

A. aerogenes with the micro-aerophilic nonhemolytic streptococcus in a mouse resulted in an abscess 1 cm. in diameter which suppurated and drained in one week.

Intradermally the *A. aerogenes* injected into a guinea pig resulted in three days in a small nodular lesion which subsided completely in one week. The streptococci alone produced in three days a similar small lesion which also subsided in one week. The two organisms injected together intradermally into a guinea pig produced in one week a 6 mm. nodule which did not drain.

Discussion

Progressive bacterial synergistic gangrene has been reported from the United States, South America, Canada, Europe, Asia and Australia.[7, 12] Most cases appearing in the American literature have been reported in surgical journals. While apparently not a common disease, it has been seen with sufficient frequency so that the non-surgical practitioner should be familiar with the clinical picture. Its occurrence in lesions other than postoperative has served to emphasize this.

This represents the second report in which an organism other than hemolytic *M. aureus* has produced the disease in a synergistic association with micro-aerophilic nonhemolytic streptococcus. On the basis of this, it may be conjectured that more cases will be observed in which *P. vulgaris, A. aerogenes, Micrococcus albus* and other organisms in the presence of micro-aerophilic nonhemolytic streptococci will be found to act synergistically to produce the disease.

In a bacteriologically confirmed case the demonstration of the efficiency of chloramphenicol and judicious local therapy indicates that this antibiotic should be given a trial in those cases unresponsive to penicillin or bacitracin before resorting to zinc peroxide and surgery. Although the response to chloramphenicol was gradual in this case, it was definite. Within four days after its initiation there was no doubt concerning the halting of the process, with regression in size of the lesion as well as a fall in the leukocyte count toward normal levels and diminution in fever. Therefore, if chloramphenicol is effective, it would seem that the change in the status of the patient will probably become obvious before too much valuable time has been lost prior to the use of surgery and zinc peroxide.

Summary

A case is presented of progressive bacterial synergistic gangrene treated successfully with chloramphenicol and local therapy without surgical intervention. Chloramphenicol is recommended in the management of this disease if penicillin and bacitracin fail.

The synergistic etiologic agents were demonstrated with animal inoculation studies to be a micro-aerophilic nonhemolytic streptococcus and *Aerobacter aerogenes.*

Summario in Interlingua

Progressive gangrena synergistic bacterial (termino proponite per Meleney) es un processo gangrenose que affice le pelle e es producite per le action synergistic de un nonhemolytic streptococco micro-aerophilic e de un altere organismo, identificate in le majoritate del reportos publicate como *Micrococcus pyogenes* var. *aureus.* Le

morbo se declara in general postoperativemente in areas cutanee circa suturas de retention, sed illo etiam occurre post vulnerationes superficial o in lesiones cutanee de longe duration.

Le aspecto clinic es satis characteristic. On nota un ulcere central con un margine de pelle gangrenose que resimila corio de Sveda e transi in un elevate zona purpurin. Iste zona, de su parte, es incirculate per erythema. Nonobstante, le morbo debe esser differentiate ab altere chronic processos gangrenose. Iste differentiation es del prime importantia proque le successo del therapia depende de illo. Le medios usate in le tractamento de iste morbo (con varie grados de successo) include extirpation chirurgic, peroxydo de zinc, penicillina, bacitracina, e chloramphenicol.

Le caso hic reportate es le secunde in que un organismo altere que *M. aureus* in association con un streptococco micro-aerophilic esseva demonstratemente responsabile pro le production del morbo. *Aerobacter aerogenes* e un nonhemolytic streptococco micro-aerophilic esseva isolate ab un lesion gangrenose de duo septimanas de duration que involveva le gamba de un feminina blanc de 32 annos de etate. Le injection combinate de iste organismos in le pelle de animales laboratorial resultava in multo plus grande lesiones que le injection individual del un e del altere.

Iste patiente respondeva a un prolongate therapia con chloramphenicol oral in doses diurne de 2 g durante 35 dies, sin chirurgia o peroxydo de zinc. Intra quatro dies post le initiation de chloramphenicol, il non esseva possibile dubitar del melioration del patiente. Isto indica que si chloramphenicol va esser efficace in un caso particular, le alteration del stato del patiente va probabilemente manifestar se promptemente de maniera que on non debe timer le risco de un grande perdita de tempore ante le uso de altere mesuras therapeutic.

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CRYPTOCOCCUS MENINGITIS IN A CASE OF CONGENITAL HEMOLYTIC ANEMIA *

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THE following case of cryptococcus meningitis is reported because of three interesting facets: its occurrence in a patient with congenital hemolytic anemia, an associated leukemoid reaction with some immature myeloid forms, and its failure to respond to large doses of cycloheximide.

CASE REPORT

A 42 year old white married housewife was studied nine months prior to admission because of recurrent bouts of asymptomatic jaundice. A diagnosis of congenital hemolytic anemia was established which, in the light of its mild manifestations, was treated conservatively. Two weeks prior to admission she developed generalized muscular and joint pains with associated low grade fever. Two days after this onset the pain localized in her sacral area. This was relieved by medication given by her physician, but at the same time she developed generalized headache, which was relieved for only brief periods through the use of morphine. Except for the occurrence of nausea and vomiting with the headache, there were no other symptoms. In particular, neurologic symptoms were strikingly absent.

Physical examination revealed a woman of approximately the stated age of 42 years, in a good state of nutrition and of normal habitus, but dehydrated, icteric and in acute distress as a result of severe headache. Temperature was 99.6° F.; pulse, 76; respirations, 20; blood pressure, 130/84 mm. of Hg. Physical examination disclosed a smooth and nontender enlarged liver, 3 cm. below the costal margin, a smooth and nontender enlarged spleen, 5 cm. below the costal margin, and nuchal rigidity.

A chest x-ray was normal with respect to lung fields and cardiac contour and size. Blood studies revealed a hemoglobin of 9.6 gm. per 100 ml., or 62.2%; red blood cells, 3,130,000 per milliliter; white blood cells, 21,000 per milliliter, with 83% neutrophils, 1% metamyelocytes, 2% myelocytes, 3% lymphocytes, 10% monocytes, 1% young monocytes, and 1% normoblasts. Smear revealed toxic granulation of

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the neutrophils and numerous spherocytes. The prothrombin time was 83% of normal. Nonfasting blood sugar (after intravenous glucose infusion) was 138 mg.%. The urine was dark orange and alkaline, with a specific gravity of 1.023, a slight trace of albumin, 0.75% glucose (during intravenous infusion of glucose), negative acetone, and revealed on microscopic examination many triple phosphate crystals and red blood cells (Foley catheter was in place), and an occasional white blood cell and epithelial cell. Cephalin cholesterol flocculation was 3 plus, and thymol turbidity was 4.9 units. The total serum bilirubin was 7.8 mg.%, and van den Bergh reaction was positive direct.

A lumbar tap revealed an opening pressure of 310 mm. of water. The fluid was opalescent, and microscopically revealed the field to be loaded with yeastlike budding organisms. Safranine, Wright's and methylene blue stain confirmed this (figure 1), and India ink preparation revealed a distinct capsule (figure 2). The

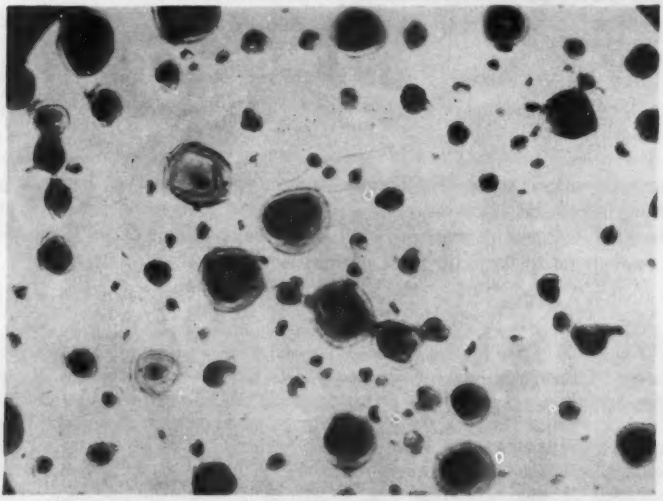

FIG. 1. Cerebrospinal fluid sediment × 900, safranine stain showing variability in size and budding forms.

cerebrospinal fluid protein was 54 mg.%; sugar, 42 mg.%; chlorides, 595 mg.%. Culture was performed on two successive taps, each of which resulted in a growth of *Cryptococcus neoformans.*

Except for nuchal rigidity, neurologic examination at this time remained normal. Subsequent lumbar punctures revealed pressures of 475, 450 and 380 mm. of water; the appearance of the fluid remained the same. In each tap just enough fluid was slowly removed to reduce the pressure to one-half of its initial level.

Because cycloheximide was not immediately available, and because of reported beneficial effects [1] of penicillin and sulfadiazine, procaine penicillin, 300,000 units intramuscularly every 12 hours, and sulfadiazine, 0.5 gm. every four hours orally, were started. Not only was there no clinical improvement but, on the contrary, the patient developed papilledema, retinal hemorrhages, and pareses of the left third and sixth cranial nerves. Within three days cycloheximide was received and therapy was initiated. After a test dose of 5 mg. intramuscularly, the patient was given 30 mg. intramuscularly every four hours for the first day and then 40 mg. every four

hours intramuscularly. There was no clinical improvement. The febrile course was mild and fluctuating. Neurologic examination revealed increased rigidity, dilated inactive pupils, complete immobility of the left eye except for internal rotation, ptosis of the left upper lid, weakness of the arms and legs, absent deep tendon reflexes, and increasing papilledema. The spinal fluid protein decreased to 40 mg.% and the sugar to 31 mg.%. The culture remained positive for *Cryptococcus neoformans*. Five days after the diagnosis was established the patient became blind. Dehydration during this period was corrected by intravenous fluids. Parenteral vitamins were given. The hemoglobin decreased to 8.7 gm. per 100 ml., or 56.3%. The white blood cells remained elevated at 26,400 per milliliter, with 89% segmented neutrophils, 1% basophils, 3% lymphocytes and 7% monocytes. Smears continued to show toxic granulation and spherocytes. Coma deepened and the patient died eight days after the diagnosis was established, which was six days after the initiation of cycloheximide therapy.

FIG. 2. Cerebrospinal fluid sediment × 900, India ink preparation demonstrating the capsule.

Postmortem Examination: Autopsy findings included terminal pneumonia (right lower lobe), chronic cholecystitis with cholelithiasis, severe passive congestion of the spleen, acute toxic nephrosis, and generalized mild arteriosclerosis. Only the central nervous system showed gross and microscopic evidence of cryptococcus infection. The brain weighed 1,330 gm. A yellowish green exudate covered the basilar aspect of the brain from the frontal lobes to the cerebellum and, to a lesser degree, the cord. The exudate was thick but small in amount, and between the cerebral hemispheres it was frankly bloody. The surfaces of the brain and the cord were slippery. There was a cerebellar pressure cone. The lenticular nucleus on the right contained several cystic spaces measuring up to 3 mm. diameter, in which *Cryptococcus neoformans* was demonstrated microscopically. The meninges (figure 3) were thickened, with little cellular reaction to the massive numbers of organisms present within them. In some areas the organisms could be seen in the Virchow-Robin spaces surrounding the smaller vessels. The ganglion cells showed toxic changes.

DISCUSSION

This case represents failure of cycloheximide by intramuscular injection to influence the relentless course of cryptococcus meningitis. In vitro cyclo-

heximide has a marked fungistatic effect,[2] and has been reported to have apparently effected a clinical cure.[3] Other reports [2, 4] have indicated that a variable response may be expected, some cases being temporarily helped, others uninfluenced, and occasionally cases are reported cured.[3] At present the value of cycloheximide is probably equivocal, inasmuch as "cures" have been reported only sporadically, and then with the use of other drugs, such as sulfadiazine.[5] In view of the generally poor response to antibiotic therapy,[4] treatment with cycloheximide is probably warranted and indicated at present.

The association of cryptococcosis in a case of hemolytic anemia is probably merely coincidental. Cases associated with Hodgkin's disease, granulocytic leukemia, lymphatic leukemia, monocytic leukemia, reticulum cell sarcoma and

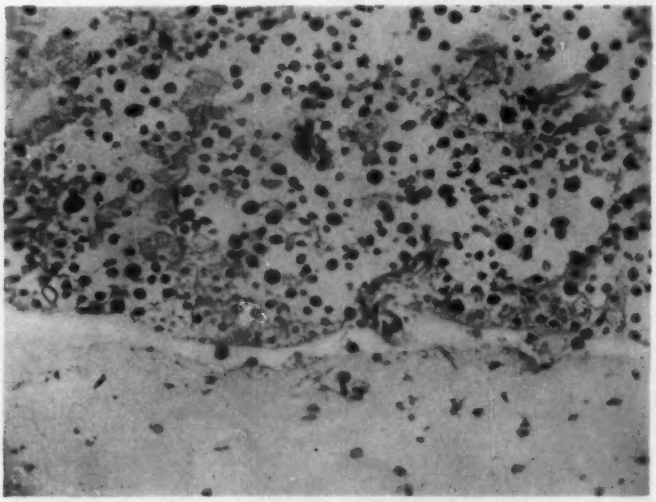

FIG. 3. Cerebrum and meninges × 200, toluidine blue stain, demonstrating the massive numbers of organisms in the subarachnoid space (upper part), with no inflammatory response in the cerebrum (lower part).

multiple myeloma have been reported.[4, 7] The presence of immature myeloid forms in the peripheral blood of this case at first seemed somewhat unusual. However, their occurrence in systemic cryptococcosis has been reported to occur, in one case to such a degree that the diagnosis of myeloid leukemia was entertained.

The involvement of only the central nervous system and meninges is not unusual. The source of infection could not be ascertained, and evidence of systemic involvement could not be found either while the patient was alive or at postmortem examination. A report that this patient had been exposed 16 months previously in Florida to an individual who allegedly was recovering from cryptococcus meningitis could not be verified, despite repeated efforts to trace the individual and the medical records.

Summary

A case of cryptococcus meningitis involving only the central nervous system and meninges is reported. Postmortem examination showed no evidence of involvement of other organs or tissues. The patient failed to respond to cycloheximide administered in large doses intramuscularly. Coincidentally, the patient represented a case of congenital hemolytic anemia.

Acknowledgment

Cycloheximide (Acti-dione) was generously supplied by Dr. Harold Reames, of the Upjohn Company, Kalamazoo, Michigan.

Appreciation is expressed to the following who participated in the diagnosis and treatment of this patient: Dr. S. Dutch, Dr. R. Griffith, Dr. W. Sawitz, Dr. H. Stempem and Dr. W. Whitely.

Summario in Interlingua

Meningitis causate per *Cryptococcus neoformans* se disveloppava in un femina de 42 annos, qui habeva essite diagnosticate circa 18 menses previemente como patiente de congenite anemia hemolytic. Le declaration del meningitis esseva acute. Al initio le suspicion esseva que il se tractava de un spontanee hemorrhagia subarachnoide. Tamen, frottis de fluido cerebrospinal demonstrava le presentia de spheric e incapsulate organismos monocellular in stato de buttonamento. Super le base de su characteristicas morphologic e cultural iste fungo esseva identificate como *Cryptococcus neoformans* (*Torula histolytica*). In despecto del therapia initial a penicillina e sulfadiazina sequite per le administration generose de Acti-diona, le patiente moriva circa quatro septimanas post le declaration del symptomas meningeal. Le examine autoptic non revelava le presentia de ulle lesiones causate per le fungo, excepte un extense leptomeningitis cerebrospinal e un numero de cystes continente le organismo in le region del capsula interne. Il non esseva possible substantiar le historia, obtenite ab le familia del patiente, del exposition repetite de illa, un anno previemente, a un persona in qui meningitis cryptococcal esseva suspicite.

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ATROPINE POISONING: REPORT OF TWO CASES *

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ALTHOUGH atropine poisoning has occasionally occurred following overdosage with suicidal intent, and after the ingestion of wild berries of *Atropa belladonna,* the great majority of reported cases have been therapeutic accidents, resulting from carelessness on the part of physicians, pharmacists, patients and unskilled hospital aides. Fortunately, mortality is uncommon because of the rapid excretion and inactivation of the drug, but the affected patients are often violently ill. After observing a near-fatal episode of poisoning in a child in 1929, Heller [1] concluded that future morbidity and mortality could be prevented by the use of the word "POISON" on bottles of atropine solution. The basic problem is unchanged today and more stringent precautions are required, perhaps in the form of improved labeling and a heightened awareness of atropine's marked toxicity. It is the purpose of the present report to reëmphasize this need, and to describe two unusual cases of acute atropine poisoning resulting from the erroneous use of ophthalmic atropine solution as intranasal medication.

CASE REPORTS

On January 6, 1954, H. H. and J. M., inmate orderlies on duty in the U. S. Penitentiary Hospital at Leavenworth, Kansas, were admitted as patients because of growing restlessness, incoherent speech, performance of bizarre acts, and complaints of thirst, nausea and dizziness. From other hospital personnel it was ascertained that, one hour previously, both men had complained of a disturbing rhinorrhea associated with a head cold. This had not responded satisfactorily to antihistaminics and ephedrine nose sprays. The patients, prompted by their imperfect knowledge of the antisecretory benefits of atropine, asked the assistant in the pharmacy for atropine nose drops. Despite information that only 2% ophthalmic atropine solution was available, they requested and received one-half medicine dropper (the equivalent of eight to 10 drops) of this preparation, placed into each nostril in a head-down (Proetz) position. It is calculated that in this manner each man received 20 to 25 mg. of atropine, an amount 25 to 30 times the maximal therapeutic dose. The solution used had been originally prepared from commercially purchased atropine powder, which had the inscription, "POISON," on the label of its container. However, as is widespread practice, the label placed on the small therapeutic bottle of atropine solution did not carry this warning. The individual progress reports follow:

Case 1 (*H. H.*). One-half hour after receiving the atropine solution this 25 year old white orderly informed several other hospital attendants that he felt nauseated and was going to the bathroom to relieve himself. It was noted at this time that his pupils were widely dilated and his face was flushed. Several minutes later the attendants found the patient unconscious in the bathroom. He was aroused and carried to a hospital bed. Despite admonitions to remain quiet, he immediately arose from the bed, stating that he had a pressing desire to urinate. A urinal was handed to him, but he disregarded this and micturated onto the floor. He soon complained of increasing thirst. His speech became thick and slurred and he had difficulty in

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expressing himself clearly. When first seen by a physician, one hour later, the patient appeared delirious and moderately agitated, waving his arms freely and muttering without significance. On several occasions, during attempted but futile questioning, he indicated that he desired to rise and go to the bathroom, but was forcibly restrained and kept in bed. Other significant findings included: temperature, 100.5° F.; pulse rate, 122 per minute; blood pressure, 130/70 mm. Hg; respirations, 20 per minute. The skin, particularly of the face, was hot, dry and flushed. The lips and buccal mucosa were parched. The pupils were widely dilated and failed to respond to light and accommodation. Deep tendon reflexes were equal bilaterally, but hyperactive. Muscular coördination was poor. On the basis of the history and physical findings, a diagnosis of atropine poisoning was made. In an effort to diminish the patient's marked psychomotor activity, he was given morphine sulfate, 15 mg. Prostigmine, 0.5 mg., was administered hourly, but was discontinued after three injections when no appreciable effect was obtained and the patient was now presenting a picture dominated by mental aberrations.

During the ensuing 24 hours the patient complained of vague pains in his chest and abdomen, and of thirst, nausea and headache. He developed transient extrasystoles, which disappeared spontaneously. His pulse and temperature elevation abated gradually. During this period he performed many strange acts suggestive of an acute psychosis, characterized by gross disorientation, confusion and visual hallucinations. He splashed water from the toilet bowl to the floor of the bathroom; moved from his bed to an adjacent bed, announcing that there were several small men forcing him to transfer; stood in the corridor of the ward stating that he was waiting for a streetcar; complained that a little man, hiding beneath his bed, sneaked up occasionally to tickle him; and identified bugs on the wall, which he attempted to kill. The patient laughed inappropriately and generally manifested a labile emotionalism. His movements were slow and clumsy. He occasionally fell into a deep sleep, with regular, stertorous breathing, but in sleep-free intervals was extremely restless and irritable. During this period he received fluids by mouth and required three injections of phenobarbital sodium, 130 mg., for sedation.

Twenty-four hours after taking the atropine solution the patient complained chiefly of nausea, considerable thirst and parching of his throat. Pulse rate was 90 per minute; temperature, 99.6° F. His face was still flushed, but his pupils were not so markedly dilated. He was kept in bed for an additional 24 hours and, except for requesting "four guitars, in case one breaks," was generally lucid and aware of his environment. Forty-eight hours after the onset of the atropine intoxication the patient appeared to be asymptomatic and was discharged. However, one week after the incident he impulsively walked away from the dining-room rather than toward it, contrary to his wish. In addition, it was determined several months later that he had developed retrograde amnesia for events occurring immediately prior to the atropine episode. There were no further abnormalities.

Case 2 (*J. M.*). About 15 minutes after receiving the atropine this 29 year old white orderly complained to a nurse of a sensation of marked dizziness and lethargy. He started to walk up and down the hall quickly, appearing perturbed and proclaiming that he could not work. He pushed away coffee which was offered to him and instead attempted to drink water from the toilet bowl. One-half hour later the patient was disturbed by blurred vision. He was directed to a bed and, when seen by the author, was lying quietly, though complaining of an exquisite dryness of his throat, difficulty in swallowing, palpitations, and an urgent desire to urinate without being able to do so. Many of his remarks revealed a dissociated ideation and a clouded sensorium. Other significant findings included: temperature 100.2° F.; pulse rate 100 per minute; blood pressure, 120/80 mm. Hg; respirations, 18 per minute. The skin, particularly of the face, was hot, dry and flushed. The

lips and buccal mucosa were parched. The pupils were widely dilated and failed to respond to light and accommodation. Deep tendon reflexes were normal and equal bilaterally. Muscular coördination was poor and gait was ataxic. During the examination the patient described an incipient, uncontrollable sensation of nervousness, for which phenobarbital sodium, 130 mg., was administered. As in the case of the previous patient, he was given three injections of prostigmine, without effect. He was maintained on a fluid diet by mouth.

During the ensuing 24 hours the patient made many trips to the bathroom but had difficulty in initiating his urinary stream and managed to urinate only a few cubic centimeters on each occasion. On returning to the ward he frequently staggered to a bed other than his own. The hospital attendants attempted to guide him, but he belligerently resisted this help. Gentle coaxing by a friend, however, was efficacious in quieting him. At one time he suddenly went to the bedside of the other patient suffering from atropine intoxication and attempted to cover him "because he appeared too cold." The patient was only mildly restless and slept most of the day. Twenty-four hours later his temperature and pulse had returned to normal and his pupils were only slightly dilated. He stated that he had been disturbed during the night by numerous frightening dreams. For the next two days the patient felt tired and weak, but was completely asymptomatic thereafter.

Comment

The site of absorption of atropine in these cases appears to have been chiefly the nasal mucosa, with some overflow undoubtedly being absorbed from the gastrointestinal tract. In cases of severe systemic reaction following the instillation of ophthalmic atropine into the intact conjunctival sac, the mucosa of the nasolacrimal duct and of the nose likewise provides the main surface for introduction into the blood stream.[2] Absorption from these sites has been found to be rapid and intermediary in speed between the subcutaneous and the oral routes of administration.[3]

Only one case [1] has previously appeared in the literature in which atropine solution prescribed for intraocular use was introduced intranasally, with subsequent intoxication. However, this preparation has also produced atropine poisoning following conjunctival instillation,[4] accidental swallowing [5] and injection into a knee joint.[6] Simple prophylactic measures, including application of pressure to the inner canthus of the eye during conjunctival instillation, increased caution in writing and in compounding prescriptions, and the use of restrictive statements on all labels (such as "POISON" and "FOR USE IN EYES ONLY") may have averted many such cases. The widespread availability of atropine and other belladonna alkaloids on pharmacy and medical cabinet shelves, in pure form and in mixtures, for ophthalmic, oral, rectal, cutaneous and subcutaneous application, promotes particular susceptibility to injudicious use. Since the observation of atropine poisoning in the two cases described above, we have learned of three additional, unpublished cases,[7] one of which also resulted from the nasal use of ophthalmic atropine solution. It is concluded that the incidence of atropine intoxication is even more frequent than is suspected.

The difference in severity of clinical response to similar dosages exhibited by our patients corresponds to previously observed variations in individual tolerance to atropine.[8] The manifestations of delirium, disorientation and visual hallucinations have been mistaken for acute alcoholic and schizophrenic psychoses,

with resultant admission of some patients to psychiatric institutions. Where the history and physical findings do not aid in establishing an exact diagnosis, hypodermic injection of methylcholine,[4c] or the instillation of a drop of the suspected patient's urine into the eye of a cat [2] may be used for confirmation. Since a physiologic antidote for the serious central nervous system effects of atropine is not available, treatment is primarily supportive. Amelioration of bothersome antisialogogic and mydriatic symptoms has been obtained with pilocarpine.

Summary

Two cases of atropine poisoning resulting from the erroneous use of ophthalmic atropine solution for intranasal medication are presented. The need for more stringent care in the utilization of this valuable drug is emphasized.

Acknowledgment

The author wishes to express his sincere appreciation to Russell O. Settle, Medical Director, U. S. Public Health Service, and Chief Medical Officer, U. S. Penitentiary, Leavenworth, Kansas, for his valuable suggestions in the preparation of this manuscript.

Summario in Interlingua

Le grande majoritate del reportate casos de invenenamento a atropina es accidentes therapeutic resultante del negligentia de medicos, pharmacistas, patientes, e inexperte adjutantes hospitalari. Pro sublinear de novo le urgentia del plus stricte precaution, nos presenta duo casos de invenenamento a atropina resultante ab le uso erronee de un solution ophthalmic de atropina como medication intranasal.

In un effortio a resolver un enoiose rhinorrhea associate con rheuma cerebral, duo prisioneros-infirmeros al hospital del Penitentiario Leavenworth demandava e recipeva un medie contator-guttas de un solution ophthalmic de 2 pro cento de atropina, administrate in cata un del duo nares, con le capite in position pendente. Es a calcular que le duo individuos recipeva assi 20 a 25 mg de atropina cata un, i.e. un quantitate que es 25 a 30 vices le maximal dosage therapeutic.

Intra 15 o 30 minutas post le administration del atropina, le duo individuos disveloppava in forma progressive le signos e symptomas classic de paralyse postganglionic e de excitation del systema nervose central. Istos consisteva de forte grados de sete, parolation indistincte, urgentia e difficultate de urination, facie purpurin, pelle sic, mydriasis, tachycardia, temperatura de basse grados, confusion, inquietude, dyscoordination muscular, e augmentate manifestationes emotional. Un del patientes exhibiva signos de acute psychosis manifeste in grossier disorientation, vivace hallucinationes visual, e le execution de actos de bizarria. Le tractamento esseva symptomatic e consisteva primarimente del uso de morphina e phenobarbital a sodium como sedativos, con prostigmina administrate additionalmente in le van effortio a blocar alicunes del effectos peripheric de atropina. Intra 24 a 48 horas le duo individuos habeva recuperate ab le acute episodio. Tamen, le patiente in qui le maladia habeva essite le plus sever, disveloppava un amnesia retrograde pro evenimentos que habeva occurrite ante le episodio del intoxication a atropina.

Le sito del absorption de atropina in iste casos pare haber essite principalmente le mucosa nasal, con—sin dubita—un certe superfluxo absorbite per le vias gastrointestinal. Ben que le litteratura cognosce non plus que un sol caso in que—como in le casos hic reportate—un solution de atropina prescribite pro usos intraocular esseva introducite via le naso con le resultato de intoxication subsequente, le mesme typo de preparato ha essite responsabile pro invenenamento atropinic post instillation conjunctival, inglutition accidental, e injection in un articulation de genu. Simple

mesuras prophylactic—le application de pression al commissura interior del oculo durante le instillation conjunctival, grande attention in scriber e executar receptas, e le uso de etiquettas con le inscription "Veneno" o "Solmente pro Uso Intraocular," etc.—ha probabilemente essite de adjuta in prevenir plus numerose casos. Tamen, il pare que le frequentia de intoxication atropinic es plus alte que lo que on crede. Il es de interesse que le manifestationes de delirio, disorientation, e hallucinationes visual ha essite erroneemente interpretate como symptomas de acute psychoses alcoholic e schizophrenic. Si le historia del patiente e le constatationes physic non suffice pro establir un diagnose exacte, le injection hypodermic de methocholina o le instillation, in le oculo de un catto, de un gutta del urina del patiente suspicite pote esser usate pro objectivos de confirmation.

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SINGLE CORONARY ARTERY: REPORT OF TWO CASES*

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We have recently observed two cases in which one coronary mouth gave rise to both the right and left coronary arteries. Although these cases are unrecognized clinically and present no characteristic evidence of their presence

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during life, they are sufficiently rare to warrant reporting. After a number of cases have been observed, perhaps some conclusions may be drawn regarding the many theories which attempt to explain their embryologic development.

Case Reports

Case 1. A 64 year old white male, night watchman for a large construction company, was found lying dead on the floor of a small shack. History obtained from a relative indicated that he had not been ill, and that he had had no complaints referable to his heart. At autopsy the cause of death was multiple old myocardial infarctions secondary to severe coronary atherosclerosis and a recent occlusion of one branch of a single coronary artery. Examination of the heart revealed it to be

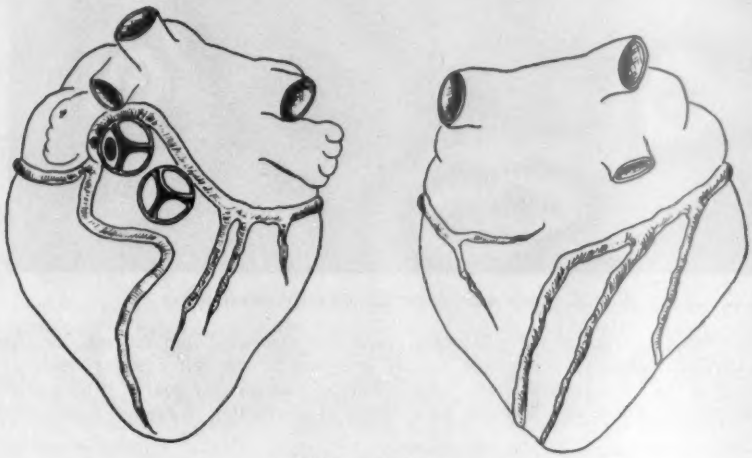

Fig. 1. Schematic diagram of single coronary artery in case 1. See text for description.

moderately enlarged, and on the left ventricle a peculiar course of a branch of a coronary artery was observed on the anterior surface of the pulmonary conus. On cut section several foci of 2 to 3 mm. areas of flame-shaped scars were found in various portions of the left ventricle in a random distribution, the most prominent one being in the anterior wall. Microscopic examination of the heart revealed these areas to be old, healed infarcts, with no evidence of fresh infarction or inflammation.

Examination of the aorta revealed the presence of only one coronary orifice (figure 1). From this ostium were four branches which opened almost directly from the single lumen. Three of these branches were large and significant. One was a rudimentary branch less than 1 mm. in size which is therefore not represented in the diagram. The large branch that courses inferiorly was designated as the left anterior descending branch of the right coronary artery. Another branch was designated as the main stem of the right coronary artery, and the upper branch was called the circumflex branch of the right coronary artery.

The left anterior descending branch of the right coronary artery was a tortuous vessel which pursued a most unusual course, in that it crossed the anterior aspect

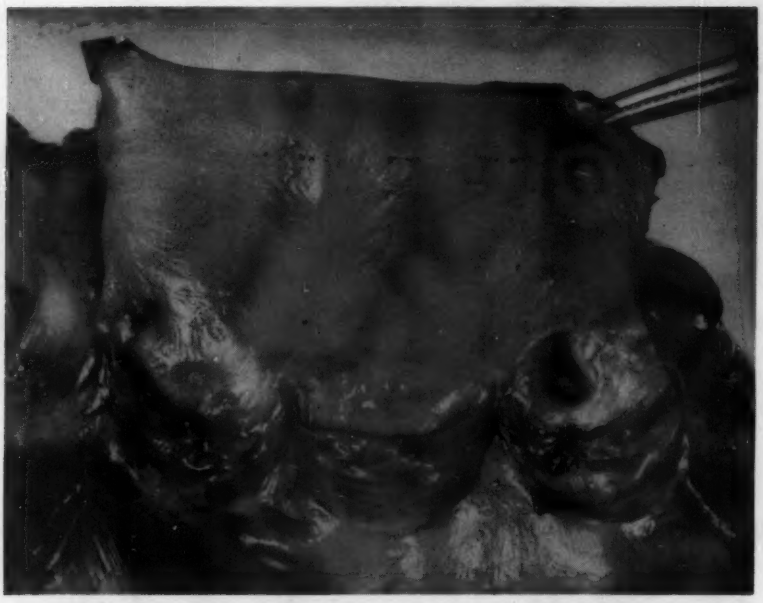

FIG. 2. Aorta with single left coronary ostium (case 2).

of the heart in front of the pulmonary conus and descended into the anterior interventricular septum in the course usually occupied by the left anterior descending branch of the left coronary artery. As a result of this peculiar course, it took several acute turns. There was, however, no evidence of obstruction or even of partial thick-

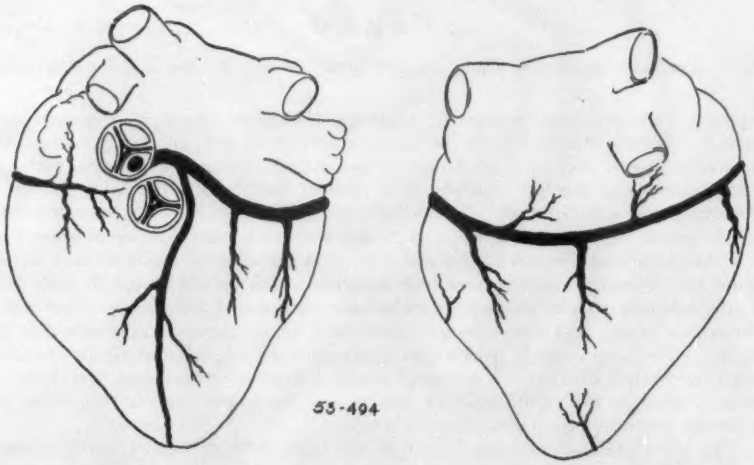

FIG. 3. Schematic diagram of single coronary artery in case 2. See text for description.

ening of the wall at any of these points. The lumen was patent and free of blood or occlusion down to its smallest ramifications.

The vessel designated as the right coronary artery was a large vessel with relatively thick walls. This pursued a rather straight course down to the sharp angle of the heart, at which point it took the usual turn of the right coronary artery. The lumen was about 2 mm. in diameter for a distance of approximately 3 cm. from the orifice, but at this point, where a small branch was given off, the lumen was markedly narrowed, if not completely occluded, by a plaque in one side of the wall. At the point of greatest bulging of the plaque into the lumen there appeared to be hemorrhage, either into the plaque or into the vessel wall. For all practical purposes the vessel appeared to be completely occluded. Microscopically the findings were hemorrhage into an atheromatous plaque in the wall, and this seemed to be in continuity with a recent thrombus in the lumen. Beyond this the lumen opened up to about 1 to 2 mm. in size, but with definite evidence of sclerosis, which was characterized by numerous calcified plaques.

The branch designated as the circumflex branch also pursued a very tortuous course and its wall contained numerous calcified plaques, particularly at the point of curvature, but there was no apparent complete occlusion. At a point about 5 to 6 cm. from the orifice it divided into two vessels, each of which down to the smallest ramifications appeared to be free of obstruction.

Case 2. A 56 year old white male whose only history was that he had been drinking on the previous night with a friend was found dead on his couch the next day when the friend came to visit him. There was no history of previous complaints of any kind. The conclusion reached at the autopsy was that he had died as a result of extensive fatty infiltration of the liver. The finding of a single coronary artery was incidental.

The heart weighed 460 gm. Dissection of the left ventricle revealed no gross abnormalities. Examination of the aorta revealed the right coronary ostium to be missing. The left coronary ostium was in the usual position, just above the left anterior aortic cusp (figure 2). From this point it passed anteriorly to divide into two large branches (figure 3). One was in the usual position of the left anterior descending branch of the left coronary artery, and the other was in the usual position of the left circumflex branch. The latter passed to the left in the atrio-ventricular fold; but instead of turning down the posterior sulcus of the heart, it continued in the atrio-ventricular fold, around the posterior aspect of the heart and again to the anterior wall, at which point its finer ramifications extended to within 1 inch of the main stem of the left anterior descending branch of the left coronary artery. In its course it gave rise to a large branch which passed down the posterior interventricular sulcus as the posterior descending branch. (It might be noted at this point that an otherwise normal left coronary artery may do this, even in the presence of both coronary arteries.) Another large branch represented the right marginal artery, arising from the circumflex. The circumflex artery terminated in several branches, some passing downward over the anterior right ventricle and one passing to the right auricle. Thus there was complete absence of the right coronary ostium and artery, and this was compensated for by a right coronary circulation, arising from the left circumflex artery. Essentially, then, there was an adequate distribution of the blood supply. The microscopic examination of the heart revealed no areas of fibrosis. The cardiac muscle fibers appeared normal.

Discussion

Most anomalies of the coronary arteries and veins are of no clinical importance, and are simply postmortem curiosities. Such examples as are com-

monly seen include extra coronary mouths, as in the case of origin of the left circumflex artery directly from the aorta, multiple coronary ostia for one artery, and an unusual course and branching of the coronary vessels. A serious anomaly is the origin of the left coronary artery from the pulmonary artery. This results in cardiac enlargement with hypertrophy and dilatation of the left ventricle, myocardial necrosis and fibrosis, and usually early death during the first few months, or years, of life.

By definition, examples of single coronary artery are those in which the entire myocardium is nourished by one artery arising by one ostium from an arterial trunk, regardless of its distribution. In 1950 Smith [1] reviewed the literature and accepted 41 cases of single coronary artery and reported two cases of his own. Since that time, to our knowledge, no case reports of single coronary artery have appeared in the literature.

Smith classified the cases reviewed by him into three types, based on embryologic considerations:

Type 1: Those in which the single vessel follows the course of only the normal right or left coronary artery.

Type 2: Those in which the single vessel arises by one ostium but divides so that branches are present in the distribution of both the right and left coronary arteries.

Type 3: Those in which the distribution of the vessel is so atypical that it cannot be compared in this regard with either the right or the left coronary artery.

On the basis of this classification Smith regarded 10 cases in the literature as Type 1, 17 cases as Type 2, and 12 cases as Type 3. In addition, he reviewed three cases which could not be grouped because of insufficient data regarding the distribution of the arteries. Our cases are characteristic of Type 2.

In attempting to explain the reasons for development of anomalies characteristic of Type 1, most authors agree that the majority of cases of single coronary artery are caused by one of two developmental anomalies. The first is a congenital absence of one coronary anlage. In cases of this type a single vessel follows the normal course of the artery it represents. As early as 1882 Hyrtl [2] stated that cases of absent coronary artery were limited to examples of this type. It was his opinion that cases in which one artery supplied the heart in the distribution of both normal right and left coronary arteries were examples of misplacement rather than absence of one coronary anlage.

Other authors [3, 4] suggested that, in the absence of one coronary artery, the remaining vessel might develop compensatory branches that would follow the course of the missing vessel and act as functional substitutes. As both of these suggestions are tenable and neither has been disproved, the distribution of the single vessel cannot be used as a criterion to distinguish absence from misplacement of one coronary anlage.

In Type 2 there is displacement of one coronary anlage, so that this anlage fuses with the first portion of the remaining normal vessel. This has been attributed to misplacement of the septum dividing the truncus arteriosus into the pulmonary artery and the aorta, with crowding together of the coronary artery anlages. Then the distribution of the single vessel is that of the normal right and left coronary arteries.

It is known that the anlages of the coronary arteries appear about the fourteenth day of fetal life, the left being formed before the right. The endothelial buds appear in the truncus arteriosus before that structure is subdivided into the aorta and the pulmonary artery by the development of the spiral septum. An aberration in the site of division by the septum might account for the anomalous origin of one or both coronary arteries from the pulmonary artery.[5] In line with the same trend of thought, it is conceivable that a dorsal deviation of the septum formed from the lateral cushions of the truncus arteriosus could crowd the anlage of the left coronary artery toward the right so that the two anlages fused.

Plaut [6] found an interesting implication of comparative anatomy in fish and amphibia, in each of which there is only one coronary vessel. Mammals as a rule have two vessels, and it therefore appears to be a late acquisition in the evolutionary process associated with separation of heart chambers.

Before the diagnosis of a single coronary artery can be made, origin of a coronary vessel from the pulmonary artery, or from a position high in the aorta, must be sought. Complete occlusion of one orifice by syphilis or by arteriosclerosis should also be excluded.

It is interesting to note that in the cases accumulated by Smith,[1] 27 occurred in adults, the average age being 45 years. The oldest was 80 years. Of these 27 cases, the cause of death was reported as related to cardiac disease in only nine. Of these nine, three exhibited a recent infarct with thrombus, and one exhibited an old infarct. On the basis of this small number of cases, it appears that the presence of only one coronary artery does not significantly alter the life expectancy of an individual. According to Master,[7] the expected incidence of myocardial infarction is about two of 28 persons dying during adult life. Consequently, one cannot theorize on hazards that might result from the presence of only one vessel.

In the report by Smith [1] there were 13 infants and one child. In nine of the 14 cases there were other anomalies of the cardiovascular system. Generally, no other cardiovascular anomalies are found in the adults possessing a single coronary artery. The authors reporting the cases of single coronary artery in infants, however, felt that it was the presence of other cardiovascular anomalies which caused their early death.

Summary

Two cases of single coronary artery are reported, making a total of 45 cases that have appeared in the literature. Since there is the unsettled question of congenital absence versus misplacement, it is preferable, at present, to record cases of single coronary artery as such, rather than as cases of anomalous origin of one coronary artery or as cases of absent coronary artery. In neither case was there any suggestion of only one coronary artery prior to examination at autopsy. The cause of death in one case was arteriosclerotic heart disease with coronary occlusion and myocardial infarction. In the second case, however, no cardiovascular disease was associated with the single coronary artery. Our present state of knowledge indicates that, in the absence of cardiovascular dis-

ease, or other anomalies of the heart, a single coronary artery is not associated with decreased cardiac function.

ACKNOWLEDGMENT

We wish to thank Miss Mary Talbot for the preparation of the schematic illustrations (figures 1 and 3) that were photographed for use in this article.

SUMMARIO IN INTERLINGUA

Isto es le reporto de duo casos de un sol arteria coronari, discoperite accidentalmente in le curso de examines autoptic. Ambe casos concerneva masculos blanc. Le un habeva 64 annos, le altere 56. Ambes revelava, ante le autopsia, nulle signo del absentia de un del arterias coronari. In un del casos le causa del morte esseva arteriosclerotic morbo cardiac con occlusion coronari e infarcimento myocardial. In le secunde caso nulle morbo cardiovascular esseva associate con le facto que le patiente habeva non plus que un sol arteria coronari. Secundo le presente stato de nostre cognoscentias, un sol arteria coronari—si non accompaniate de morbo cardiovascular o de altere anomalias del corde—non resulta in un dysfunction cardiac. Nos presenta nostre reporto del duo casos insimul con illustrationes schematic que servi a clarificar nostre description del curso del unic vaso coronari. Quando observationes ab un numero additional de tal casos deveni disponibile, il va forsan esser possibile deducer certe conclusiones in re le multiple theorias que essaya explicar le disveloppamento embryonic de iste condition.

Pro establir le diagnose del presentia de un sol arteria coronari, le derivation de un vaso coronari ab le arteria pulmonar o ab un puncto al alto del aorta debe esser disprovate. Etiam le complete occlusion de un orificio in consequentia de syphilis o arteriosclerosis debe esser excludite.

In individuos qui ha attingite un etate adulte, le condition del unic arteria coronari es generalmente associate con nulle altere anormalitate cardiac. In juveniles qui mori con un sol vaso coronari, il pare que le morte prematur es attribuibile al presentia de altere anormalitates cardiac. Il pare que le superviventia probabile, tanto in adultos como etiam in juveniles, non es reducite per le presentia per se de un sol arteria coronari. Un caso reportate in le litteratura concerne un individuo de 80 annos de etate. Le etate median inter adultos es 45 annos. Inter 27 casos adulte reportate, solmente 9 habeva morbo cardiac como causa del morte. In iste casos le morte esseva apparentemente non connectite con le presentia de un sol vaso coronari. Le numero total del reportate casos de unic arterias coronari in adultos e juveniles es 43.

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ACUTE SUPPURATIVE ARTHRITIS DUE TO *ESCHERICHIA COLI* SEPTICEMIA *

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Escherichia coli is rarely the causative organism of acute suppurative arthritis. Many reviews in the literature on acute suppurative arthritis [1-4] contain no mention of *E. coli*. Furthermore, arthritis, even in nonsuppurative form, is an uncommon manifestation of *E. coli* septicemia.[5] In 1913 Luger [6] described the case of a 43 year old man with a history of gonorrhea who developed an acute nonsuppurative polyarthritis during an episode of colibacillemia which was probably secondary to a gall-bladder infection. In 1920 Widal, Lemierre and Brodin [7] cited the case of a 25 year old woman who developed *E. coli* septicemia and a swollen right elbow (nonsuppurative) four days postpartum. Cattan [8] in 1936 reported the case of a 48 year old woman who had a polyarthritis and an *E. coli* pyelonephritis with colibacillemia. Many joints were involved but only one, the right knee, appeared to be suppurative. Its pus contained an organism suggestive of gonococcus. At post mortem a healing gonococcal endocarditis was found, as well as multiple abscesses in the spleen and liver caused by *E. coli*. In 1938 Graber-Duvernay [9] discussed a case of chronic nonsuppurative arthritis in a 36 year old woman with chronic pyelonephritis due to *E. coli*. The four reports cited above would raise the question of possible etiologic association between *E. coli* septicemia and arthritis. However, this association, on a basis of sepsis and subsequent pyemic arthritis, is not warranted from the data in these four cases because of the coexistence of gonorrhea in two of the cases and the lack of direct bacteriologic evidence from joint fluid in any of the cases. The possibility still remains that the joints may be involved on a toxic basis in *E. coli* sepsis, rather than as a result of metastatic seeding.

In 1942 Bauer, Ropes and Short [10] described acute suppurative arthritis of the left ankle caused by the colon bacillus in a 35 year old man who had a past history of gonorrhea and chronic pyuria. *E. coli* was cultured from the urine and left ankle but not from the blood. The arthritis responded slowly to therapy consisting of sulfathiazine, but repeated cultures of the urine continued to grow out *E. coli* even after the arthritis had subsided. In 1951 Miller and Engle [11] reported a case of a 55 year old woman with purulent arthritis of both knees due to *E. coli* and nonhemolytic streptococci, with periarticular gas formation, which did not respond to streptomycin, penicillin and surgical drainage. This patient, too, had a chronic pyelonephritis, and *E. coli* was cultured from the urine. At post mortem, *E. coli* was also grown from the heart's blood. The latter two reports represent the only cases known to us in which *E. coli* was proved to be the etiologic agent of purulent arthritis.

It is our purpose to report an additional case of acute suppurative arthritis with positive blood cultures caused by *E. coli* and cured by streptomycin.

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Case Report

A 24 year old white married female secretary was first admitted to Beth Israel Hospital on August 2, 1953, because of pain in the right arm, and pain and swelling of the right knee, of one day's duration. The patient had bruised her right knee following a fall about two weeks prior to admission. She had been otherwise well until the morning of the day before admission, when she awakened "not feeling well." By afternoon she noted generalized muscular aches, and that night had a shaking chill and a severe aching sensation in her right arm. She slept fitfully because of five chills and pain in the right arm and knee. By the morning of admission she noted excruciating pain in the right knee and found that it was swollen. Past history was not contributory.

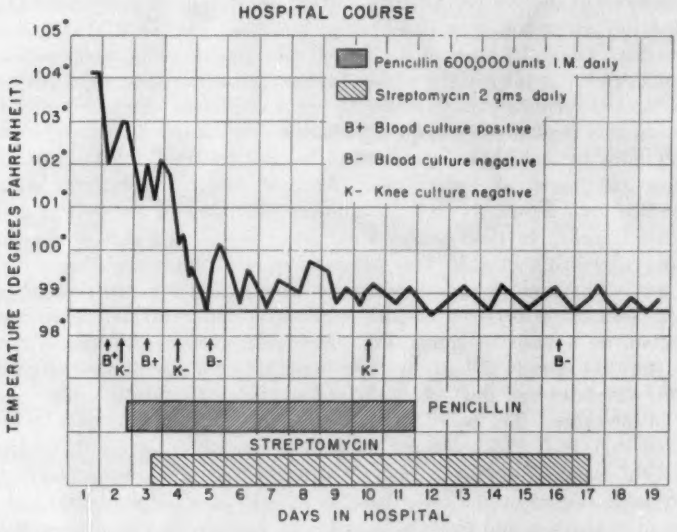

Fig. 1.

Physical examination at the time of admission revealed a temperature of 104° F.; respirations 18 per minute; pulse rate, 92 per minute; blood pressure, 120/70 mm. of Hg. The patient appeared acutely ill and pale. She was moderately lethargic, possibly due to an injection of Demerol just prior to admission. She complained of pain in her right arm and knee. The skin was hot and dry; no petechiae were noted. The conjunctivae were slightly injected. Marked photophobia was present. Small, nontender posterior cervical nodes were noted bilaterally. The lungs were clear to percussion and auscultation. The heart was not enlarged; a grade II apical systolic murmur was present. The abdomen was soft and nontender; no organs or masses were palpable. No costovertebral angle tenderness was elicited. Pelvic and rectal examinations were not remarkable except for a scant vaginal discharge. The right arm resisted motion because of muscular pain and tenderness over the biceps. No warmth or swelling was noted in this area. The right lower extremity was kept immobile. The knee was swollen, hot, fluctuant and tender but not red.

Laboratory Data: Urinalysis was normal. Hemoglobin was 11 gm.; white

blood cell count was 12,000, with 69% polymorphonuclear leukocytes, 2% stab forms, 26% lymphocytes, and 3% monocytes. Erythrocyte sedimentation rate was 27 mm./hr. (Westergren). The following blood chemical determinations were performed and found normal: fasting blood sugar, nonprotein nitrogen, uric acid, serum proteins, cholesterol, bilirubin, cephalin flocculation, alkaline phosphatase and thymol turbidity. Tests for the following antibodies were normal: typhoid, paratyphoid, brucella agglutinins, and antistreptolysin. Electrocardiogram, chest roentgenogram, plain film of the abdomen, and roentgenograms of the right shoulder and humerus were normal. The only x-ray abnormality was some swelling of the soft tissues around the right knee.

Course in Hospital (figure 1): Since the primary diagnosis considered on admission was infectious arthritis of unknown etiology, numerous cultures were taken. Culture and smear of the cervix were negative for gonococci; nose and throat cultures revealed *Staphylococcus albus,* rare coliform organisms and *Micrococcus catarrhalis;* urine culture was sterile. A blood culture was taken on the morning of the second hospital day, and that afternoon the right knee was aspirated of 50 c.c. of thick greenish yellow pus. This material had a specific gravity of 1.019. It contained many polymorphonuclear leukocytes, with numerous intracellular and extracellular gram-negative rods. The pus was left in the incubator overnight and cultured the next morning. Meanwhile, therapy was started with 300,000 units of penicillin intramuscularly twice a day. The next morning, the third hospital day, the blood culture was reported as showing hundreds of colonies per cubic centimeter of typical *E. coli,* highly sensitive to chloramphenicol and streptomycin (disc method). Culture of the exudate was sterile, probably because the incubation of the exudate overnight at 37° C. before culturing had permitted proteolysis of the organisms. After the positive blood culture was reported, a second blood culture was taken which also showed a heavy growth of an identical *E. coli.* Before the report of the second blood culture was received the therapy was changed to include 1 gm. of streptomycin twice daily by intramuscular injection. After treatment with streptomycin was initiated, two other blood cultures on the fifth and fifteenth hospital days were sterile. The temperature fell to normal and the patient improved rapidly over the period of 24 hours following the onset of streptomycin therapy. Her course was uneventful after this time. Active rehabilitation of the knee was begun on the sixth hospital day, and ambulation was achieved on the ninth hospital day. In an attempt to find a cause for the septicemia, a gall-bladder roentgenographic series and intravenous pyelograms were done during the convalescent phase. Both studies were normal. The patient had recovered completely after two weeks of streptomycin therapy and was discharged on the nineteenth hospital day, the twentieth day after the onset of illness.

Discussion

Consideration must be given to the underlying mechanism leading to the production of the acute suppurative arthritis in this case, since no focus of infection was found. It is well known that there are three possible ways for an organism to invade a joint space:[1] (1) direct wound of the joint; (2) extension of the infection from a neighboring area, and (3) hematogenous spread. The patient had bruised her knee about two weeks prior to the onset of the acute symptoms which led to her admission. This minor trauma was apparently insufficient for direct penetration by the organism, but may have predisposed the joint for future localization. Also, it is not likely that an infection of the skin, resulting from the injury, extended to the joint cavity and secondarily

produced septicemia. It is therefore probable that the knee was infected by way of the blood stream from a focus in another part of the body. Furthermore, hematogenous spread is the most common of the three mechanisms underlying infectious arthritis,[1] and this patient's illness began with symptoms referable to a generalized infection. It was indeed consistent with the picture of *E. coli* septicemia.

Neter [12] in 1886 was the first to report a case of *E. coli* sepsis, and it has been recognized quite commonly since then.[5, 13, 20] The syndrome is characterized by the appearance of an atypical infection which may be insidious or acute in onset. Malaise, myalgia, chills and high remitting fever, as well as herpes labialis, are common features of this illness. Jaundice is quite frequently observed. Leukocytosis and pulse rate commensurate with the fever are likely to be present. The diagnosis will not often be made except by demonstrating the colon bacillus on culture of the blood. Davis and Turner [13] state that 20% of cases with *E. coli* septicemia manifest metastatic pyogenic infections which can involve the skin, thyroid, kidney, liver, spleen or endocardium. In addition, meningitis [14] and suppurative arthritis [10, 11] have been reported secondary to colibacillemia. The most important of the numerous complications that follow *E. coli* sepsis is the involvement of the liver and the kidney. The mortality of colibacillemia prior to the introduction of antibiotics was variously listed at from 22 to 44%, with the ultimate prognosis dependent upon the severity of the local infection acting as a seeding focus.

There is usually an underlying source or portal of entry in the biliary tract, gastrointestinal system, uterus or urinary passages, particularly the prostate after catheterization. For this reason it is of interest that pretreatment cultures of the cervix and urine in this patient were negative, and roentgenographic studies of the gall-bladder and kidneys did not reveal a possible source of infection. No investigation of the gastrointestinal tract was done, and it is therefore not definitely possible to rule out this system in that regard. However, the patient had no symptoms or signs referable to this system. It is quite clear that the two cases of Bauer et al.[10] and Miller and Engle [11] had symptoms related to an *E. coli* septicemia, with the urinary tract as a portal of entry and the infected joints as a consequence of hematogenous spread.

The case described here represents the first instance of an apparent cure of an *E. coli* suppurative arthritis with streptomycin. It should be noted, of course, that this patient was treated with penicillin as well as streptomycin, and the possible beneficial effects of the former drug cannot be denied. However, in view of the known refractoriness of gram-negative rods to penicillin, it seems quite reasonable to ascribe the excellent therapeutic response to the addition of streptomycin, to which the organism displayed a high in vitro sensitivity. To our knowledge, no other comparable cases have been reported. Streptomycin has been utilized in other *E. coli* infections associated with *E. coli* septicemia, such as meningitis.[15, 16, 17] Worms and Vernant [18] attempted unsuccessfully to use this agent to treat a case of endocarditis associated with colibacillemia. Streptomycin has been applied successfully to the therapy of *E. coli* pyelonephritis.[13, 19] This is pertinent to a consideration of *E. coli* septicemia only because, as has been pointed out above, urinary tract infections are one of the commonest portals of entry for *E. coli* septicemia.

Summary

1. A case is presented of a 24 year old woman with *Escherichia coli* septicemia complicated by suppurative arthritis of the right knee.

2. The patient recovered promptly under a regimen including streptomycin and penicillin.

3. The rarity of any type of arthritis associated with *E. coli* septicemia is emphasized by a review of the pertinent literature.

Summario in Interlingua

Le autores presenta le caso de un 24-enne femina con septicemia a *Escherichia coli*, complicate per arthritis suppurative del genu dextere. Le relation de iste acute morbo a un contusion del mesme articulation suffirite duo septimanas previemente es questionabile. *E. coli* esseva culturate duo vices ab specimens de sanguine del patiente sed pro rationes de character probabilemente technic, ille organismo non esseva identificate in le pus que esseva aspirate ab le articulation del genu. Colorate frottis fresc de iste exsudato purulente monstrava, del altere latere, numerose gram-negative bacillos intra- e extracellular. Le recuperation esseva prompte sub tractamento con streptomycina e penicillina. Le active rehabilitation del articulation del genu esseva comenciate le septime die del morbo. Le patiente ambulava le decime die e esseva dimittite ab le hospital le vintesime die post le declaration del morbo.

Le autores discute le tres possibile vias per que un organismo pote invader un spatio articular. Illos es (1) un vulnere directe del articulation, (2) extension ab un infection vicin, e (3) diffusion hematogenic. Le tertie de iste vias es le plus commun. In le presente caso illo es le plus probabile. Nonobstante, il non esseva possibile in iste caso incriminar ulle del quatro commun entratas usate per *E. coli*, i.e. le via biliari, le systema gastrointestinal, le utero, e le vias urinari.

Septicemia a *E. coli* esseva primo reportate in 1886, sed depost iste data illo ha essite recognoscite satis communmente. Le autores presenta un delineation summari de su normal aspectos clinic. Un revista del litteratura pertinente serviva a sublinear le raritate del occurentia de ulle typo de arthritis—suppurative o altere—in iste condition.

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EDITORIAL

THE RÔLE OF AMMONIA IN CLINICAL SYNDROMES

In the latter part of the nineteenth century an operation to shunt portal blood around the liver was developed by Eck. The advantage of using this operation to study liver function in the experimental animal was recognized by a number of investigators. By 1893, it was known that a dog, operated upon in this manner, could no longer tolerate a high protein diet.[1] A characteristic syndrome developed after a short time. The dog became irritable, then would walk with a staggering gait, lifting its feet high and slapping them down on the floor. As forced meat feeding continued, the animal appeared blind, and wandered aimlessly about. Finally, it became stuporous and often had convulsions. If the meat feeding continued, the animal would die. If meat were withheld, the dog usually survived, symptom-free.

The possible rôle of ammonia derived from catabolism of proteins in the production of symptoms was considered by these investigators, and, indeed, they were able to reproduce the syndrome with ammonium chloride or sodium carbamate (a complex of carbon dioxide and ammonia). Blood ammonia levels were studied, but methods were inadequate and results were inconclusive.

These penetrating observations were submerged in a debate based on inadequate methods for the determination of ammonia, and a further consideration of ammonia as a cause of neurological syndromes was undertaken only about 30 years later, when the studies of Parnas and Embden on the formation of ammonia in muscle spurred the development of sensitive methods for the analysis of blood ammonia.[2] In France, it was demonstrated that fish were poisoned by ammonia at concentrations approaching the levels found in hepatic disease [3] and other workers showed that protein decomposition by ammonia forming organisms in the gut was the main source of the ammonia found in the blood.[4] Van Caulaert showed that the administration of ammonium salts or urea in amounts tolerated by normal

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[2] Parnas, J. K.: Biochem. Ztschr. **155**: 247, 1925.

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[3] Hugounenq, M. M., and Florence, G.: Notes de laboratoire sur les derives de quelques acids amines, Compt. rend. Soc. de chim. biol. **3**: 174, 1921.

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individuals caused typical hepatic coma in patients with Laennec's cirrhosis.[5] This was probably the first time that coma was deliberately provoked in human beings by feeding ammonium ions or precursors. In Germany, it was demonstrated that liver failure was associated with inability to utilize ammonia, and an ammonia tolerance test was proposed as a test of liver function.[6] Parnas found that the blood ammonia rose in many disease states such as shock, poisonings, and anoxia, and on severe exertion.[7]

In the United States, Kirk conducted a painstaking investigation of the metabolism of ammonia by normal patients and by those with hepatic disease.[8] He came to the conclusion that the inability of cirrhotics to clear ammonia from the blood was related to the shunts they developed around the liver. A further conclusion that was reached in this study was that blood ammonia had no relation to hepatic coma, even though the two patients who got the highest blood levels of ammonia after ingesting ammonium salts both went into coma. This work was accepted as the final word on ammonia and liver disease until the group at Boston City Hospital again showed the effect of urea and ammonia on the mental state of patients with cirrhosis.[9] Further studies in the Massachusetts General Hospital showed a clear correlation between the administration of protein, urea, ammonium chloride, and ammonium resins and the development of characteristic mental and electroencephalographic charges in a cirrhotic patient with an Eck fistula.[10] The increasing use of liver shunting operations for the treatment of esophageal varices [11] stimulated interest in the problem of hepatic coma and many studies of blood ammonia were undertaken. Some confusion was injected into the picture by observations in England by Walshe and Senior [12] that there was a rise in sulfhydryl groups in the blood in some patients with hepatic coma, and that methionine administration precipitated coma somewhat better than ammonium chloride. The sug-

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[10] McDermott, W. V., Jr., and Adams, R. D.: Episodic stupor associated with Eck fistula in human with particular reference to metabolism of ammonia, J. Clin. Investigation **33**: 1, 1954.

[11] Whipple, A. O.: Rationale of portacaval anastomosis, Bull. N. Y. Acad. Med. **22**: 251, 1946.

[12] Walshe, J. M., and Senior, B.: Disturbances of cystine metabolism in liver disease, J. Clin. Investigation **34**: 302, 1955.

gestion was made that methyl mercaptan (the sulfur analogue of methyl alcohol, derived from methionine) was the toxic agent in hepatic coma. The findings were not consistent, however, and could not explain the development of coma by cirrhotics on non-methionine containing diets. By chemical methods [13] methyl mercaptan and dimethyl sulfide have been detected in the urine of patients with fetor hepatis. There is thus little doubt that when it occurs, the fetid odor of the breath and urine is caused by these derivatives of methionine. On the other hand, fetor hepatis is only an infrequent sign in hepatic coma.

Sherlock's group showed a relation between blood ammonia level and symptoms of coma, with considerable overlap among various levels.[14] The same group very elegantly demonstrated an affect of antibiotics on the intestinal flora, inhibiting production of ammonia, and correlated this with the improvement shown by cirrhotics in coma on oral antibiotics. A similar phenomenon had been demonstrated by Terroine and Lauresco [15] and was also shown in the case of McDermott and Adams.[10] The conclusion to be drawn from this consensus is that oral antibiotic therapy, adequate to diminish the bacterial flora of the gut, can be expected to have some value in the handling of hepatic coma or precoma states.

Since there is some controversy regarding the rôle of ammonia in the production of hepatic coma, it might be well to review the evidence. There is, in general, agreement that protein or its derivatives can initiate or exacerbate coma in the patient with severe liver damage. The finding of Sherlock that methionine seems to precipitate coma more effectively than other amino acids or ammonium salts, together with data that sulfhydryl compounds are elevated in the blood in hepatic coma, suggests a possible etiological rôle for methionine in the process. Admittedly, however, this is neither invariably present in coma, nor, for that matter, is it usual. Furthermore, it is possible to reproduce all of the symptoms with any metabolizable source of nitrogen including ammonium acetate and even ion exchange resins in the ammonia cycle, which, when ingested orally can exchange ammonia for sodium or potassium. If one is to consider the etiologic agent to be anything other than ammonia, then the position must be taken that ammonia exerts its toxicity by being converted to an intermediate closer to protein, and then acting to produce coma. Since protein catabolism results in free ammonium as the proximal intermediate for half of the nitrogen excreted (half of the urea nitrogen is derived from ammonia), the most likely probability is that ammonia itself is the toxic agent.

[13] Challenger, F., and Walshe, J. M.: Methyl mercaptan in relation to foetor hepaticus, Biochem. J. **58**: xxviii, 1954.

[14] Sherlock, S., Summerskill, W. H. J., White, L. P., and Phear, E. A.: Portal systemic encephalopathy: neurological complications of liver disease, Lancet **2**: 453, 1954.

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There is some evidence obtained by ammonia determinations on venous blood, which, in a number of cases, fails to show a relation between the blood ammonia level and the symptoms. Many reasons exist for such lack of correlation. In the first place, it has now been demonstrated that the muscle removes about 50% of the blood ammonia coming to it.[16] This utilization of ammonia is sufficient to mask the actual ammonia content of the arterial blood, which is the blood bathing the brain. It is impossible to predict what the arterial level of ammonia will be, given the peripheral venous value. A second cause of discrepancy between blood ammonia and clinical symptoms is the difficulty in establishing a clear cut case of hepatic coma. Generally, there are complications which affect the brain such as subarachnoid hemorrhage, alcoholism, and uremia. These cause symptoms very similar to hepatic coma, and they must be excluded. Foley and Adams [17] described a rough tremor of the hands, the so-called "flapping tremor," which they claimed was a characteristic sign of hepatic coma. We have observed and recorded such tremor in uremia. In fact, uremia is one of the most difficult syndromes to separate from the true hepatic coma. Although it might be expected that the blood urea nitrogen would be low in hepatic failure, since the sole urea synthesizing organ is the liver, a low blood urea nitrogen is not a necessary concomitant of hepatic failure. It is essential to the clarification of this problem that we recognize the dynamic relation between synthesis and excretion of urea. If the urea synthesis rate is equal to the renal excretion rate, the blood urea nitrogen will remain constant. If hepatic disease resulting in a 50% impairment in urea synthesis develops, the excretory power of the kidney for urea might be diminished by a like amount. In this case the blood urea content would remain normal.

If, however, renal failure results in a greater impairment of urea excretion than loss of hepatic function, there will be a rise in the blood urea nitrogen, even though an absolute deficiency in urea synthesis exists. Furthermore, the patient with liver failure is subject to prerenal azotemia resulting from variceal bleeding or hemorrhage from prothrombin or fibrinogen depletion. The "hepatorenal syndrome" was a popular diagnosis a decade ago and has been interpreted in many ways. There is no doubt that renal failure does accompany hepatic failure. In this situation, it is necessary to recognize the source of the coma in order to institute rational therapy. For example, administration of serum protein might be indicted in renal failure and is contraindicted in hepatic failure. For this reason, a clear concept of the mechanism of hepatic failure is necessary.

There is one criterion for hepatic coma which is invariably absent in renal failure, and that is an elevated blood ammonia concentration. The usual finding in uremia is a normal or low blood ammonia. In the normal

[16] Bessman, S. P., and Bradley, J. E.: Uptake of ammonia by muscle, New England J. Med. **253**: 1143, 1955.

[17] Adams, R. D., and Foley, J. M.: The neurological disorder associated with liver disease, Research Publ., A. Nerv. and Ment. Dis. **32**: 198, 1953.

individual, a considerable amount of ammonia is introduced into the circulation by the kidney, incidental to the renal excretion of ammonia. Since the renal synthesis of ammonia is impaired in disease of the kidney, the urinary tract does not contribute its share to the blood ammonia content. The proposition is therefore made that a worthwhile basis for differentiating or identifying the nature of coma in a patient with hepatic and renal disease is a determination of the blood ammonia content. As a corollary, it might be possible that a number of cases called hepatic coma in the literature and shown to have low blood ammonia content might well have been cases of uremia in patients with liver disease.

A final cause for the discrepancy between blood ammonia levels and depth of coma might be found in the chemical mechanism for the production of coma by ammonia. It has been postulated that the excessive ammonia in the blood reverses (by mass action) certain reactions in brain which normally produce ammonia.[18] This would lead to a depletion of intermediates in the oxidative (Krebs) cycle, and should be demonstrable as a utilization of ammonia by brain. Evidence for such a phenomenon has been obtained in patients by the demonstration that the brain actually uses ammonia when the blood level is elevated. If there is a finite amount of such oxidative intermediates in brain, it could be exhausted rapidly by reactions resulting from a high blood ammonia or slowly in the face of a less marked, but chronically elevated blood ammonia. The important feature of the rôle of ammonia in the pathogenesis of hepatic coma is that attrition of the oxidative mechanism takes place and that as long as such attrition occurs, it cannot be repaired. Using this concept it is possible to understand how a patient with a slightly elevated blood ammonia could, over a long period, develop as much of a depletion of essential cerebral metabolites as can occur with a higher blood ammonia level over a shorter time. The toxicity is thus a product of ammonia excess and duration. Some interesting data from Greenstein's laboratory show that the interval before lethal doses of amino acids exert their effect on rats is inversely proportional to the rate of rise of the blood ammonia in these animals.[19]

Sodium glutamate has been suggested by Walshe [20] as a therapeutic agent in hepatic coma. Its effect could be mediated in two ways—first, it could combine with ammonia to form glutamine, which transports ammonia

[18] Bessman, S. P., and Bessman, A. N.: Cerebral and peripheral uptake of ammonia in liver disease with hypothesis for mechanism of hepatic coma, J. Clin. Investigation **32**: 622, 1955.

Bessman, S. P., and Bessman, A. N.: Ammonia poisoning of hepatic coma—cerebral arteriovenous amino acid levels, Lancet **2**: 336, 1954; and Fed. Proc. **13**: 336, 1954.

[19] Gullino, P., Winitz, M., Birnbaum, S., Cornfield, J., Otey, M., and Greenstein, J. P.: The toxicity of individual essential amino acid mixtures with special reference to the protective effect of l-arginine, Arch. Biochem. and Biophys. **58**: 255, 1955.

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[20] Walshe, J. M.: The effect of glutamic acid on the coma of hepatic failure, Lancet **1**: 1075, 1953.

to the kidney for excretion; second, a mechanism for the therapeutic effectiveness of glutamate would be by transamination with pyruvic acid, normally formed by glucolysis to provide alpha-ketoglutaric acid, an intermediate of the Krebs cycle. Unfortunately, these reactions cannot take place in brain because glutamate cannot pass the blood brain barrier, and, in fact, their major activity is in the liver. It is therefore not surprising that glutamate is effective in only certain "types" of hepatic coma. An attempt was made to differentiate forms of hepatic coma on the basis of their response to glutamate.[21] One type of coma, amenable to glutamate, occurred with variceal bleeding or was provoked by protein feeding. Another type, refractory to glutamate, occurred spontaneously on a low protein diet. All that this differentiation shows is that there are various degrees of liver damage. If the enzymatic structure of the liver is so damaged that even the minimal ammonia produced on a low protein diet is enough to cause irreversible accumulation of ammonia in the blood, then the glutamate reactions *in the liver* cannot be expected to help the patient since they too must be seriously damaged. On the other hand, if the patient carries on well and can only be put into coma by excessive nitrogen intake, his liver enzymes are probably not so seriously damaged, and glutamate can help him, through the liver metabolism which remains. Glutamate should, therefore, be tried in any case, but it is not an answer to hepatic coma. Some other means for lowering the toxic ammonia levels must be sought, and this might well be through some technic of replacing Krebs cycle intermediates in the brain itself. Successful sodium glutamate therapy appears to depend upon the presence of a considerable amount of functional integrity of the liver.

Were it only in hepatic coma that catabolic ammonia exerted its toxic effect, it might not be of such general interest. It is clear, however, that the blood ammonia is elevated in many other situations, whether or not the liver is grossly damaged. For example, A. N. Bessman and Evans have shown that the blood ammonia is elevated in heart failure.[22] It has long been recognized that poor oxygenation is not usually the cause of mental symptoms associated with chronic passive congestion. These workers showed a parallel between blood ammonia and mental state.

Seligson [23] showed a sharp rise in blood ammonia in shock and Parnas [24] pointed out, 30 years ago, that the most constant change occurring in the blood at death was an immediate rise in ammonia content, anoxia and stasis causing rapid evolution of ammonia from the muscles. This is not the

[21] McDermott, W. V., Jr., Wareham, J., and Riddell, A. G.: Treatment of "hepatic coma" with l-glutamic acid, New England J. Med. **253**: 1093, 1955.

[22] Bessman, A. N., and Evans, J.: Blood ammonia in congestive heart failure, Am. Heart J., 1955.

[23] Nelson, R. M., and Seligson, D.: Studies on blood ammonia in normal and shock states, Surgery **34**: 1, 1953.

[24] Parnas, J. K., and Klisiecki, A.: Über den Ammoniakgehalt und die Ammoniakbildung im Blute. VI, Biochem. Ztschr. **173**: 224, 1926.

same phenomenon observed in heart failure, since the muscles take up ammonia in the coma associated with that condition.

The rôle of ammonia in the production of mental symptoms resulting from excessive return of urea to the gut as in implantation of ureters into the colon [25] has to be documented further, as do Fuld's [26] observations on increased blood ammonia in diabetic coma and lobar pneumonia.

Our own observations [27] reveal the presence of excessive ammonia in the blood in certain pediatric conditions such as erythroblastosis fetalis, where it may contribute to the development of kernicterus.

The recent report on the increased ammonia content of the blood on administration of acetazoleamide (Diamox) to patients with liver disease explains the well known toxicity of this drug to patients with hepatic functional impairment.[29] Clinical experience with this drug can provide valuable insights into the metabolism of ammonia, and furthermore, other drugs active in renal metabolism might influence blood ammonia. It is not certain, however, that the effect of this drug on blood ammonia is actually mediated through the kidney.

One of the most interesting aspects of ammonia metabolism, and the one with the most clinical significance, is the fact that there are so many reactions by which ammonia is made in the organism, and so few ways to dispose of it.[28] This results in a great number of opportunities for excessive production of ammonia to take place, and the limited number of pathways for its disposal makes the organism particularly susceptible to deleterious factors. The marked effect of ammonia on brain metabolism in vivo together with the ubiquitous production of this toxic agent makes a plausible case for ammonia as a causative or contributing factor in many of the comatose states associated with peripheral disease.

S. P. BESSMAN.

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[26] Fuld, H.: Über die diagnostische Verwertbarkeit von Ammoniakbestimmungen im Blut, Klin. Wchnschr. **12**: 1364, 1933.

[27] Bessman, S. P.: In preparation.

[28] Bessman, S. P., *in* McElroy, W. V., and Glass, H. B.: Ammonia metabolism in animals. Inorganic nitrogen metabolism, Johns Hopkins Press, Baltimore, Maryland, 1955.

[29] Webster, L. T., Jr., and Davidson, C. S.: Production of impending hepatic coma by a carbonic anhydrase inhibitor, Diamox, Proc. Soc. Exper. Biol. and Med., **91**: No. 1.

REVIEWS

Surgery of Pulmonary Tuberculosis. By JAMES H. FORSEE, A.B., B.S., M.D., F.A.C.S., F.A.C.P., Colonel, M.C., U. S. Army; Chief, Surgical Services, Fitzsimons Army Hospital, Denver, Colorado. 208 pages; 15.5 × 24 cm. Lea & Febiger, Inc., Philadelphia 6, Pa. 1954. Price, $6.50.

This is one of the first books in recent years dealing primarily with surgical treatment of pulmonary tuberculosis. Since the advent of streptomycin, approximately seven years ago, and the other drugs effective in the treatment of pulmonary tuberculosis, the overall therapy has undergone many startling changes.

The very broad topic headings of both collapse therapy and extirpative surgical therapy are discussed in concise terms. Explanation is made of the rôle played by chemotherapeutic agents, when used as adjuncts with extirpative surgery, which actually makes it possible.

The author has arranged the information in the book into three major divisions. Part I relates to the principles used as a basis for applying surgical treatment for pulmonary tuberculosis. Part II encompasses the operative surgical procedures and includes a variety of technics and methods used. Part III deals with the author's experience with surgical therapy in pulmonary tuberculosis. Many statistical data have been prepared by Col. Forsee from studies done at Fitzsimons Army Hospital. These data are both interesting and enlightening. The case follow-up method used and the evaluation of results are both particularly well done and in the final analysis actually point out the trends in surgical therapy.

The graphs and tables are both meaningful and easily interpreted. The illustrations are of good quality.

R A. C.

Subacute Bacterial Endocarditis. Publication No. 274, American Lecture Series. By ANDREW KERR, JR., M.D. 343 pages; 14.5 × 22.5 cm. Charles C Thomas, Springfield, Illinois. 1955. Price, $6.50.

This monograph by Andrew Kerr, Jr. presents a compilation of all the important literature, as well as his own observations, on the now somewhat less dreadful but still often elusive disease, subacute bacterial endocarditis. The volume represents the first effort at a formalized text on the subject and will, because of its wealth of statistical data, undoubtedly be a much used reference.

One of the most interesting parts of this rather complete work is the historical section devoted to early observations and writings, and credits to some of the most outstanding names in the history of medicine. There is probably no other subject which has interested such an array of talent.

The clinical aspects of the disease from definition to special consideration are presented in a sequential manner that makes cover to cover reading easy. All previously mentioned aspects of the entity are evaluated as to frequency of occurrence by analysis of the large number of well documented series of case reports. Statistical reports in long form become cumbersome at times but are probably more meaningful in context. It appears that there is no facet of the problem that is not given its just consideration. Latest reports on experimentally produced disease are included.

The section on therapy will remind the reader that the prognosis is not as greatly altered with the advent of the bactericidal and bacteriostatic agents as is generally considered. Therapy that has met with the greatest success is outlined and cause of failure discussed.

Because of the multiple ways in which this disease may present and the importance of early diagnosis, everyone will find it rewarding to acquaint himself with the information contained in this work. Now that adequate therapy frequently results in cure, and prophylaxis in prevention, awareness of the facts is more important than ever. The clouding of diagnosis by indiscriminate use of bacteriostatic agents should be reëmphasized. There is no group which can consider itself immune to its consideration.

A. R.

Thrombosis and Embolism: Proceedings of the I International Conference, Basel, 1954. Edited by TH. KOLLER and W. R. MERZ. 1316 pages; 18 × 25 cm. Benno Schwabe & Co., Basel. 1955. Price, Gebunden Fr. 76.

This is a six pound book of over 1300 pages containing the works presented at the first international conference on Thrombosis and Embolism held at Basel in 1954. It contains 254 contributions in three languages. Every paper is followed by a brief summary in French, English and German.

The matter was divided into 16 groups of subjects including the physiology and patho-physiology of coagulation, chemistry and pharmacology of anticoagulants, pathogenesis and patho-physiology of thrombosis and several chapters on the clinical aspects and therapy of thrombosis.

There is then material for everybody: pure "coagulationists," pharmacologists, pathologists, general practitioners and thoracic surgeons.

Many of the participants to the Congress are outstanding students of this field.

It is a fact that our knowledge of the diseases characterized by lack of coagulability of the blood is more extensive than that of the diseases characterized by hypercoagulability, even though the latter are of far more practical importance. This book reflects this deficiency of knowledge. The subject of the pathogenesis and patho-physiology of thrombosis, that should represent the core of the Congress, is developed in 35 papers, many of which are of clinical character. They show the efforts of human ingenuity to investigate this phenomenon but also they show the inadequacy of our technical possibilities in this field.

The greater part of the book is then devoted to the other subjects listed above, namely physiology of coagulation, anticoagulants and the clinical aspects of thrombosis.

In our opinion, then, the importance of this Congress and this book lies mostly in the exposition of the progress in the practical management of the patients suffering from thrombosis and in the stimulus given to more basic research in the field of the specific patho-physiology.

GIOVANNI RACCUGLIA, M.D.

Cancer Cells. By E. V. COWDRY. 677 pages; 16.5 × 25.5 cm. W. B. Saunders Company, Philadelphia. 1955. Price, $16.00.

The author has succeeded in producing a stimulating textbook on the significant features of the cancer cell. Skillfully compounded and balanced, this edition contains an immense amount of facts, statistics and thoughts about many types of cancer from various viewpoints.

The first five chapters are technical and deal chiefly with the microscopic and biochemical characteristics of malignant cells as compared to benign tumor cells. The internist not oriented to microscopy will find ample examples and explanations of the morphologic changes occurring within the cytoplasm and nuclear substance.

The major portion of the text has a clinical import in that many problems en-

countered in everyday medicine are discussed. Wherever possible, examples of human cancer are cited to illustrate certain theories; the major portion of the experimental studies, by necessity, has been made in animals. The chapters on carcinogens and viruses as causative factors make exciting reading.

The problem of familial tendency to cancer is clarified. The author believes that common malignancies occurring in a single family are much more likely due to chance than to genetic transmission or group exposure to particular carcinogens. In a family of 10 members the probability that none will develop cancer is one in five; that one will develop cancer is one in three; and that three members out of 10 will have cancer, surprisingly, is one in eight. Only in the rare tumors such as retinoblastoma is there a definite familial incidence far exceeding the chance occurrence.

The concluding chapters are directed to age and sex differences, geographical variances, problems in diagnosis, treatment and prevention of cancer. An extensive and well-chosen bibliography of over 2200 references is a great asset. The author, calling frequently upon his years of experience in cancer research, expresses his opinion on the work and findings of others. These comments not only add information to an already informative text, but they should be of assistance to anyone laboring with the voluminous literature. An appendix lists the various cancer registries, organizations, international journals and other important publications.

This book is a convenient reference for all interested in cancer, experimental or clinical; it should be of special interest to pathologists and cytologists. The reader is made to feel the full impact of cancer research, its urgency, its future problems, and the ever-prevailing hope that the cause and cure of cancer will be found. This book is highly recommended.

HOWARD F. RASKIN

Counseling in Medical Genetics. By SHELDON C. REED, Director, Dight Institute for Human Genetics, The University of Minnesota. 268 pages; 20.5 × 14 cm. W. B. Saunders Company, Philadelphia. 1955. Price, $4.00.

Few physicians have had training in medical genetics, though most physicians are called upon from time to time for advice concerning the chance that certain human abnormalities will be inherited. The purpose of this small book by the Director of the Dight Institute for Human Genetics of the University of Minnesota is to help the physician answer such questions from his patients.

In the first three brief chapters the author summarizes the development of interest in human genetics, the types of problems brought to the physician, and the character of the reactions in parents and relatives to the presence of an inheritable abnormality. Following this introductory matter there is an admirable but short discussion of the basic laws of human heredity and their application in twins and in the marriage of blood relatives.

Thereafter the major portion of the book is devoted to specific genetic problems ranging from various types of mental deficiency and different forms of insanity, through skin color, congenital dislocation of the hip, allergies, blood groups, diabetes, etc. Only the commoner problems are dealt with in the text, but in the appendix there is reproduced the listing of rarer traits originally assembled by Fraser.

The book is written in a semi-popular style. It is very readable, clear and practical. In the opinion of the reviewer it fills a real need and will be of value to all medical students and clinicians.

M. C. P.

Heart Disease, Its Diagnosis and Treatment. 2nd Ed. By EMANUEL GOLDBERGER, M.D., F.A.C.P., Associate Attending Physician, Montefiore Hospital, and Attending Physician, Lincoln Hospital, New York; Lecturer in Medicine, Columbia University. 781 pages; 15.5 × 24 cm. Lea and Febiger, Philadelphia. 1955. Price, $12.50.

This is an expanded, revised edition of a text dealing with heart disease. It contains a great deal of information, and many useful facts and statements concerning heart disease. However, one does not get a sense of perspective by reading this book, and the relative importance of various procedures, etc. does not seem to be weighed as carefully as it might be. There are a number of statements with which one may disagree, such as the statement that fluoroscopy should be done with the infant lying if possible, that penicillin is contraindicated in acute rheumatic fever, the author's overly cautious attitude toward the use of digitalis in acute rheumatic fever, and his comparatively radical attitude toward interruption of pregnancy in patients with heart disease. This volume is an improvement over the previous edition.

S. S.

BOOKS RECENTLY RECEIVED

Books recently received are acknowledged in the following section. As far as practicable those of special interest will be selected for review later, but it is not possible to discuss all of them.

Androgens: Biochemistry, Physiology, and Clinical Significance. By RALPH I. DORFMAN, Ph.D., Associate Director of Laboratories, Worcester Foundation for Experimental Biology, etc.; and REGINALD A. SHIPLEY, M.D., Director, Radioisotope Unit, Veterans Administration Hospital, Associate Professor of Medicine, Western Reserve University School of Medicine. 590 pages; 24 × 15.5 cm. 1956. John Wiley & Sons, Inc., New York. Price, $13.50.

Blood Group Substances: Their Chemistry and Immunochemistry. By ELVIN A. KABAT, Departments of Microbiology and Neurology, College of Physicians and Surgeons, Columbia University, etc. 330 pages; 23.5 × 15.5 cm. 1956. Academic Press, Inc., New York. Price, $8.00.

Borderland Problems Between Physical Chemistry and Physiology. Monograph Series of the Research Institute of Applied Electricity, No. 5 (1955). Edited by Y. ASAMI, Professor of Electrical Engineering, Director of the Research Institute of Applied Electricity, Hokkaido University; and K. HIGASI, Professor of Physical Chemistry, Hokkaido University. 130 pages; 26 × 18 cm. (paperbound). 1955. The Research Institute of Applied Electricity, Hokkaido University, Sapporo, Japan.

Diagnosis of Congenital Heart Disease: A Clinical and Technical Study by the Cardiologic Team of the Pediatric Clinic, Karolinska Sjukhuset, Stockholm. By SVEN R. KJELLBERG, EDGAR MANNHEIMER, ULF RUDHE and BENGT JONSSON. 649 pages; 26.5 × 18.5 cm. 1955. The Year Book Publishers, Inc., Chicago. Price, $22.00.

Diseases of the Liver. Edited by LEON SCHIFF, M.D., Ph.D., Professor of Clinical Medicine, University of Cincinnati, College of Medicine, etc.; with 27 contributing authors, and with a Foreword by CECIL J. WATSON, M.D., Ph.D. 738 pages; 26 × 18.5 cm. 1956. J. B. Lippincott Company, Philadelphia. Price, $16.00.

Ergebnisse der Medizinischen Grundlagenforschung. Band I. Herausgegeben von K. Fr. Bauer. 855 pages; 26.5 × 18.5 cm. 1956. Georg Thieme Verlag, Stuttgart; available in the U. S. A. and Canada from Intercontinental Medical Book Corporation, New York. Price, Ganzleinen DM 129.–

Experimental Tuberculosis: Bacillus and Host, With an Addendum on Leprosy. Ciba Foundation Symposium. Editors for the Ciba Foundation: G. E. W. Wolstenholme, O.B.E., M.A., M.B., B.Ch.; and Margaret P. Cameron, M.D., A.B.L.S.; assisted by Cecilia M. O'Connor, B.Sc. 396 pages; 21 × 14.5 cm. 1955. Little, Brown and Company, Boston. Price, $9.00.

Farmacologia Materia Medica y Terapeutica. Tomo I. By Luis E. Camponovo and Alfredo J. Bandoni. 644 pages; 23.5 × 16 cm. 1955. Lopez & Etchegoyen, S.R.L., Buenos Aires.

Joint FAO/WHO Expert Committee on Meat Hygiene: First Report. World Health Organization Technical Report Series No. 99. 52 pages; 24 × 16 cm. (paper-bound). 1955. World Health Organization, Geneva; available in U. S. A. from Columbia University Press, International Documents Service, New York. Price, 60¢.

Mechanisms of Congenital Malformation: Proceedings of the Second Scientific Conference of the Association for the Aid of Crippled Children, June 15 and 16, 1954. Chairman: Dr. S. R. M. Reynolds, Department of Embryology, Carnegie Institution of Washington. Harold Wolff, Editor, New York City, N. Y. Editorial Committee: Dr. Joseph Dancis, Department of Pediatrics, New York University College of Medicine; Dr. S. R. M. Reynolds, Department of Embryology, Carnegie Institution of Washington; and Dr. Clement A. Smith, Department of Pediatrics, Harvard Medical School. 137 pages; 23.5 × 15.5 cm. 1955. Association for the Aid of Crippled Children, New York. Price, $3.00.

Practitioners' Conferences Held at The New York Hospital-Cornell Medical Center. Vol. 3. Edited by Claude E. Forkner, M.D., F.A.C.P., Professor of Clinical Medicine, Cornell University Medical College, etc. 293 pages; 22 × 14.5 cm. 1956. Appleton-Century-Crofts, Inc., New York. Price, $6.75.

Retrolental Fibroplasia Rôle of Oxygen: Report of the Sixteenth M & R Pediatric Research Conference. 62 pages; 23 × 15 cm. (paper-bound). 1955. Issued by M & R Laboratories, Columbus, Ohio. Available on request.

Shock and Circulatory Homeostasis: Transactions of the Fourth Conference, December 6, 7, and 8, 1954, Princeton, N. J. Edited by Harold D. Green, M.D., Professor of Physiology and Pharmacology, and Associate in Internal Medicine, Bowman Gray School of Medicine, Wake Forest College, Winston-Salem, N. C. 291 pages; 23.5 × 16 cm. 1955. Sponsored by the Josiah Macy, Jr. Foundation, New York. Price, $5.00.

Symposium on Myasthenia Gravis: Papers Read at the First International Conference on Myasthenia Gravis at Philadelphia, Pa. on December 8–9, 1954, under the Auspices of the Myasthenia Gravis Foundation, Inc., New York. Guest Editors: Henry R. Viets, M.D., and George D. Gammon, M.D. 88 pages; 27 × 19.5 cm. (paper-bound). 1955. Reprinted from Vol. 19, Nov., 1955, *The American Journal of Medicine;* distributed by The Myasthenia Gravis Foundation, Inc., New York. Limited number of reprints still available, on request.

Your Blood Pressure and How to Live With It. By William A. Brams, M.D.; illustrations by Hertha Furth. 160 pages; 21 × 14.5 cm. 1956. J. B. Lippincott Company, Philadelphia. Price, $2.95.

COLLEGE NEWS NOTES

News Notes for the Annals

Members and subscribers to the Annals of Internal Medicine are invited to send in any news items of interest in the field of internal medicine. Information concerning coming events, such as meetings, postgraduate courses, scholarships, honors, awards, etc., or personal items about members of the College should be submitted at least two to three months in advance of publication. News items close on the 10th of the second month preceding publication. Please make such notes in all detail, names, dates and places. Send them to the News Editor, American College of Physicians, 4200 Pine St., Philadelphia 4, Pa.

New Life Members

The College is gratified to have as new Life Members the following Fellows:

Dr. Milton Shaw, Lansing, Mich.
Dr. Max Millman, Springfield, Mass.
Dr. Thomas A. Pitts, Columbia, S. C.
Dr. Abraham S. Gordon, Brooklyn, N. Y.
Col. Donald B. Peterson, (MC), USA, Washington, D. C.
Dr. Julian C. Gant, Madison College, Tenn.
Dr. Carroll L. Birch, Chicago, Ill.
Dr. Merl L. Margason, Portland, Ore.
Dr. Glenn I. Hiller, Highland Park, Mich.
Dr. William Horowitz, New York, N. Y.
Dr. Edward Schons, St. Paul, Minn.

Gifts to College Library of Publications by Members

The College expresses its heartfelt appreciation to the following members who have presented autographed copies of their books to the College Library of Publications by Members:

James R. Lisa, M.D., F.A.C.P., New York, N. Y.—*Cancer of the Lung,* co-authored with Milton B. Rosenblatt, M.D.
Walter Modell, M.D., F.A.C.P., New York, N. Y.—*The Relief of Symptoms.*
John H. Talbott, M.D., F.A.C.P., Buffalo, N. Y.—*Collagen Diseases,* co-authored with R. Moleres Ferrandis, M.D.
John H. Talbott, M.D., F.A.C.P., Buffalo, N. Y.—*Gout and Gouty Arthritis.*
John H. Talbott, M.D., F.A.C.P., Buffalo, N. Y.—*Gout.*
Andrew Kerr, Jr., M.D., (Associate), Syracuse, N. Y.—*Subacute Bacterial Endocarditis.*

Summary of the Survey on Education in Allergy

With the support of the New York Community Trust, the American Foundation for Allergic Diseases has recently completed surveys on education in allergy. One dealt with undergraduate, the other with graduate and post-graduate facilities.

I. *Undergraduate Education:* Returns from 70 medical schools were analyzed by Dr. Giles A. Koelsche, from whose report a summary of pertinent information has been drawn. This shows that over one-third of the schools reporting provide

no allergy training with 12 of the schools not reporting at all, in spite of the fact that all but 5 of the 70 reported that they have allergy clinics. Again, of the 70 institutions, only 12 reported that their allergy clinic was "approved" for residency or fellowship training by the American Boards.

One-half of the institutions reported that members of their faculty, other than those directly concerned with allergy, had some major research or clinical interest in the allergic problems. Again, in one-half of the institutions, instruction in allergy was limited to about 7 hours altogether, although the opportunity was afforded by option to work in the clinic or in the wards, on allergy problems in 81% and finally funds for research in allergy from various sources existed in only 43 of the reporting institutions, whereas in other special fields, there were funds in 85%. However, it is not clear from this report just what proportion of the latter funds in related fields might be working on problems directly or indirectly related to allergy. In one-half of the institutions reporting, there had been some, but slight increase in allergy instruction over the past five years.

II. *Graduate and Post Graduate Education:* The replies from 85 medical schools and institutions to which was added some published data on approved programs were reviewed by Dr. Richard A. Kern. Of particular interest are some of the comments of his analysis. For example, the total number of residencies and fellowships for graduate training appears to be 40 (7 of them in federal hospitals), 34 of which in 18 different institutions are "approved" by the American Boards. Dr. Kern further states and I quote directly from his report:

"The significant *evidences of progress* are: an increase in the total number of residencies and fellowships (40 vs. 31), an increase in approved residencies and fellowships (34 vs. 24), an increase in institutions with such programs (24 vs. 17) and an increase in institutions with *approved* programs (18 vs. 12).

"At this point, attention is called to two further aspects of the education of physicians with regard to allergy.

"The first has to do with *the graduate training of specialists in internal medicine and in pediatrics.* It is axiomatic that a properly trained internist or pediatrician must have some practical knowledge of the clinical manifestations of allergy, their recognition and their management. Therefore it should be required that residency training in these two fields include the routine assignment of trainees to a period of service in the allergy clinic of the hospital, for experience with allergic patients, by far the greater number of whom are ambulatory. Yet of the 85 institutions listed in Table I, only 8 (U. of California at Los Angeles, Howard U., State U. of Iowa, U. of Minnesota, Washington U., Temple U., Baylor U., and the U. of Wisconsin) require residents (medical in 6 schools, pediatric in 2) to serve a term of duty in the allergy clinic. In addition, such service is elective at 5 schools (U. of Chicago, Tulane U., Johns Hopkins U., the State U. of New York at Syracuse, and the U. of Pennsylvania). Although there may be such training in the allergy clinics of schools that failed to reply, it is clear that this phase of training in allergy is being seriously neglected.

"Then there is the matter of the *post-graduate type of instruction in allergy for practicing physicians,* especially those in general practice, but also applicable to certified allergists requiring such instruction. Table I shows that 12 schools (George Washington U., Cook County Graduate School of Medicine, U. of Kansas, Hansel Foundation, Columbia U., State U. of N. Y. in N. Y. C., N. Y. Polyclinic Medical School, Hahnemann Medical College, Temple U., U. of Pittsburgh, U. of Texas and U. of Washington) make some recurring effort in this direction by means of "refresher" courses. Here, too, the available information must be very incomplete. Nevertheless, there is great need for extension and expansion of such programs."

The Foundation plans to continue from time to time surveys with an improved questionnaire and with better technics, following some of the excellent suggestions that Dr. Kern has made. It is our hope that this brief summary of the recent surveys will provoke not only interest but some action on the part of medical schools, the deans and the professors of medicine and pediatrics as well as the directors of institutions concerned with medical education, for it is evident that there is room for improvement in education in the field of allergy (sensitization) which is of great and growing importance to medicine.

ROBERT A. COOKE, M.D., Chairman
Scientific and Educational Council
of the American Foundation for
Allergic Diseases

WESTERN ASSOCIATION OF PHYSICIANS FORMED

During the past year a new medical society, the Western Association of Physicians, was formed. Its objectives are to provide meetings for persons with an established, active rôle in clinical research. Experimentation will be conducted with different types of scientific reports. Many of the essayists will present not only their recent investigations but also summaries of progress in their respective fields. The scientific programs for the Western Association of Physicians, for the Western Society for Clinical Research and for the Western Section of the American Federation for Clinical Research are to be integrated.

The first meeting of this Association was held Jan. 25, 1956, in Carmel, Calif., under the presidency of Dr. Robert H. Williams, F.A.C.P., Professor of Medicine, University of Washington. The officers of the Association for 1956–57 are Maxwell M. Wintrobe, F.A.C.P., Professor of Medicine, University of Utah, President; T. L. Althausen, F.A.C.P., Professor of Medicine, University of California, Vice-President; Joseph F. Ross, F.A.C.P., Associate Dean and Professor of Medicine and Radiobiology, Treasurer; and David A. Rytand, Professor of Medicine, Stanford University, Clement A. Finch, Professor of Medicine, University of Washington, John S. Lawrence, F.A.C.P., Professor of Medicine, University of California at Los Angeles, and Gordon Meiklejohn (Associate), Professor of Medicine, University of Colorado, Councilors.

EXAMINATIONS BY CERTIFYING BOARDS

The American Board of Internal Medicine, William A. Werrell, M.D., Executive Secretary-Treasurer, 1 W. Main St., Madison 3, Wis. Written Examination, Oct. 15. Oral Examinations: Los Angeles, April 12–14; Chicago, June 7–9; and New York City, Sept. 21–25.

The American Board of Dermatology and Syphilology, B. M. Kesten, M.D., 1 Haven Ave., New York 32, N. Y. Written Examinations: Various centers, July 26. Oral Examination: St. Louis, Oct. 12–15.

The American Board of Pediatrics, John McK. Mitchell, M.D., Executive Secretary, 6 Cushman Rd., Rosemont, Pa. Oral Examinations: Cincinnati, Ohio, June 8–10; New York City, Oct. 12–14; and San Francisco, Calif., Dec. 7–9.

The American Board of Physical Medicine and Rehabilitation, Earl C. Elkins, M.D., 200 First St., S.W., Rochester, Minn. Parts I and II: Chicago, June 16–17.

The American Board of Radiology, B. R. Kirklin, M.D., Kahler Hotel Bldg., Rochester, Minn. Chicago, June 5–9, and Los Angeles, Sept. 30–Oct. 4.

Examinations in Sub-Specialties

The American Board of Internal Medicine will hold examinations in the Subspecialty of Cardiovascular Disease, June 6, in Chicago, Ill. Further information may be obtained by writing to the Executive Secretary-Treasurer, William A. Werrell, M.D., 1 W. Main St., Madison 3, Wis.

Submission of Titles for A.C.P. 1957 Session

The Committee on Educational Policy of the Board of Regents has suggested that the Fellows and Associates of the College be invited to submit titles of abstracts (not to exceed 200 words) of papers to be considered for the Annual Session of the American College of Physicians at Boston, Mass., April 8–12, 1957. Consequently, all Fellows and Associates are invited to submit titles and abstracts to the President, Dr. Walter L. Palmer, 950 E. 59th St., Chicago 37, Ill., prior to Aug. 1, 1956. Presumably it will be possible to place on the program of the 1957 Session in Boston only a small portion of the papers submitted. It is hoped, however, that the plan will bring to light many subjects and speakers who might be overlooked, and also that some information will be offered recording current interests. Suggestions may thus arise for symposia, panel discussions, morning lectures, clinics, and the afternoon sessions.

A.C.P. Postgraduate Courses

Spring 1956 Schedule

Nine courses by the College were scheduled between January 1 and June 30, 1956. Six of these courses will have been concluded by the appearance of this announcement, as follows:

Recent Advances in Cardiovascular Disease: Southwestern Medical School of The University of Texas, Dallas, Tex.; Carleton B. Chapman, M.D., F.A.C.P., and Maurice M. Scurry, M.D., F.A.C.P., Co-directors. 57 registrants; a new course on the College schedule; well received.

Selected Subjects in Internal Medicine: Columbia University College of Physicians and Surgeons, New York, N. Y.; Franklin M. Hanger, M.D., F.A.C.P., and Robert F. Loeb, M.D., F.A.C.P., Co-directors. 116 registrants; this was a repeat of a previous course; a most successful and rewarding course.

The Heart: Recent Advances in Diagnosis and Treatment: University of Kansas Medical Center, Kansas City, Kans.; E. Grey Dimond, M.D., F.A.C.P., Director. 50 registrants; a new course on the College schedule; well received.

Isotopes in Clinical Medicine: Ohio State University College of Medicine, Columbus, Ohio; Charles A. Doan, M.D., F.A.C.P., William G. Myers, Ph.D., M.D., F.A.C.P., and Bruce K. Wiseman, M.D., F.A.C.P., Co-directors. First week, 3A, orientation course, 20 registrants; second week, 3B, practical, detailed, individual laboratory exercises, 14 registrants. 3B was intended to be limited to a maximal of 10 registrants in order to give practical laboratory work and to qualify the registrants to fulfill present A.E.C. requirements; a superb course for those interested in this special field.

Radiology in Internal Medicine: University of Oregon Medical School, Portland, Ore.; Charles Dotter, M.D., Director, and Howard P. Lewis, M.D., F.A.C.P., Co-director. A new course on the College schedule; maximal of 25 registrants, with several applicants turned away; the first time a course has been organized in the

College for training the internist in essential knowledge of radiology; a practical and well-received course.

SOME RECENT DEVELOPMENTS IN PRINCIPLES AND PRACTICE OF MODERN INTERNAL MEDICINE: Pennsylvania Hospital, Philadelphia, Pa.; Garfield G. Duncan, M.D., F.A.C.P., Director. A repeat of a course given on several previous occasions; final registration figures not yet available, but maximal registration of 100 is assured; a top notch course.

Courses Yet to Be Given

No. 6, ADVANCES IN ELECTROCARDIOGRAPHY: New York University-Bellevue Medical Center, New York, N. Y.; Charles E. Kossmann, M.D., F.A.C.P., Director; June 4–8, 1956. A new course on the College schedule; registration limited to 40; very greatly oversubscribed.

No. 7, ENDOCRINOLOGY: Tufts University School of Medicine at the New England Center Hospital, Boston, Mass.; Edwin B. Astwood, M.D., F.A.C.P., Director; June 18–23, 1956. Designed for the internists who are especially interested in endocrinology and who desire further training in the basic physiology and biochemistry of the subject. Faculty includes, in addition to local authorities in Boston, a number of specialists from other parts of North America, each of whom is an expert in his field. Emphasis will be placed on the fundamental sciences contributing to endocrinology and will deal with recent advances in clinical endocrinology. Registration still open.

No. 8, MODERN CONCEPTS OF INTERNAL MEDICINE: State University of Iowa College of Medicine, Iowa City, Iowa; William B. Bean, M.D., F.A.C.P., Director; J. Maclean Smith, M.D., F.R.F.P.S. (Glas.), Associate Director; George N. Bedell, M.D., and William P. Jolly, M.D., Assistant Directors; June 18–22, 1956. A new course on the College schedule; while the course is directed toward modern concepts of internal medicine, a moderate amount of emphasis will be placed on cardiology and recent improvements in treatment and diagnosis in the general field of internal medicine. Teaching will be carried out by a combination of lecture, seminar, round table conference, clinical pathological conference and the presentation of many cases. Registration still open; up to 100 registrants can be accommodated.

Autumn 1956 Schedule

The Committee on Postgraduate Courses will be ready to announce the autumn schedule in the advertising section of this journal, June, 1956, number. The Committee will have concluded the schedule at its meeting held during the Annual Session of the College at Los Angeles in April, but their decisions are not available at the time of the preparation of this announcement. Under consideration, however, are courses in Internal Medicine at Vanderbilt University School of Medicine, Nashville, Tenn., under Doctors Rudolph H. Kampmeier, F.A.C.P., and Hugh J. Morgan, M.A.C.P.; at Emory University School of Medicine, Atlanta, Ga., under Doctor Eugene B. Ferris, F.A.C.P.; at the University of Washington School of Medicine, Seattle, Wash., under Doctor Robert H. Williams, F.A.C.P.; a course in Ballistocardiography at Johns Hopkins Hospital, Baltimore, Md., under Doctor Benjamin M. Baker, Jr., F.A.C.P.; courses in Gastro-enterology either at the University of Pennsylvania Graduate School of Medicine, Philadelphia, Pa., under Doctor Henry L. Bockus, F.A.C.P., or at Boston University School of Medicine, Boston, Mass., under Doctor Franz J. Ingelfinger; a course in Hematology at Washington University School of Medicine, St. Louis, Mo., under Doctor Carl V. Moore, F.A.C.P., or at Tufts University School of Medicine, Boston, Mass., under Doctor William Dameshek, F.A.C.P.; a course in Cardiology at the National Heart Institute, Washington, D. C.

Definitely scheduled is RECENT ADVANCES IN CARDIOVASCULAR DISEASES, at Mt. Sinai Hospital, New York, N. Y., under the direction of Doctors Arthur M. Master, F.A.C.P., and Charles K. Friedberg, F.A.C.P. (October 8–12, 1956).

Preliminary Postgraduate Bulletin will be distributed to all members early in July and the Final Bulletin will be published about September 1.

AMERICAN COLLEGE OF PHYSICIANS POSTGRADUATE COURSE

COURSE No. 8—MODERN CONCEPTS OF INTERNAL MEDICINE (June 18–22, 1956), State University of Iowa College of Medicine, Iowa City, Iowa. *Director,* WILLIAM B. BEAN, M.D., F.A.C.P.; *Associate Director,* J. MACLEAN SMITH, M.D., F.R.F.P.S. (Glas.); *Assistant Directors,* GEORGE N. BEDELL, M.D., WILLIAM P. JOLLY, M.D. (Minimal Registration, 25; Maximal Registration, 100.) Fees: A.C.P. Members, $30.00. Non-members, $60.00.

This is a new course on the College schedule. Not for many years has there been an ACP sponsored course at the State University of Iowa. It has been organized for members of the American College of Physicians, but other internists with adequate background of training and experience may be accepted.

A moderate amount of emphasis will be placed on cardiology and also on recent improvements in treatment and diagnosis in the general field of Internal Medicine. Teaching will be carried out by a combination of lecture, seminar, round table conference, clinical pathological conference and the presentation of a large number of cases.

Meeting Place: University Hospitals, Medical Amphitheater, Room E331.

Hotel Accommodations:

Jefferson Hotel, 107 S. Dubuque Ave., Iowa City, Iowa; single rate, $3.00 and $3.25; double rate, $6.75 (bath), and $8.00.

Blue Top Motel, Highway 6 West, Iowa City, Iowa; single rate, $4.00; double rate, $5.00.

Motel Iowa, Highway 6 West, Iowa City, Iowa; single rate, $4.50; double rate, $5.50.

Pine Edge Motel, Highway 6 West, Iowa City, Iowa; single rate, $4.50; double rate, $6.00.

Hawkeye Lodge, Highway 6 West, Iowa City, Iowa; single rate, $5.00; double rate, $6.50.

When writing for reservations, identify yourself with the American College of Physicians and this particular course.

Registration: All registrations must be filed with the American College of Physicians, 4200 Pine St., Philadelphia 4, Pa.

Outline of Course

Monday, June 18

A.M. Session

9:00– 9:10 Welcome.
Dr. Bierring.

9:10– 9:20 Orientation.
Dr. Smith.

9:20–10:20 Epidemiology of Arteriosclerosis.
Dr. Keys.

10:20–10:40 Coffee Break.

10:40–11:00 Questions.

11:00–11:30 Certain New Concepts of Electrocardiology.
Dr. January.

11:30–12:00 Clinical Ballistocardiography.
Dr. Martt.

12:00–12:30 Indications for Cardiac Surgery.
Dr. Theilen.

12:30– 2:00 Lunch.

P.M. Session

2:00– 3:30 Technical Aids in the Diagnosis of Difficult Cardiac Lesions.
Round Table Conference.
Moderator: Dr. Culbertson.
Drs. Van Epps, January, Martt, Theilen and Wild.

3:30– 3:45 Intermission.

3:45– 4:30 Surgery for Septal Defects.
Dr. Ehrenhaft.

4:30– 5:30 Clinic—Hypertension.
Moderator: Dr. Kirkendall.
Drs. Culbertson and Meyers.

Evening Session
7:30– 8:15 Radioisotopes in Clinical Medicine.
Dr. Peterson.
8:15– 9:15 Clinic—Conservative Treatment of Acute Renal Failure.
Drs. Kirkendall, Martt, and R. Smith.

Tuesday, June 19

A.M. Session
9:00–10:00 Treatment of Thyrotoxicosis with Radioiodine.
Dr. DeGowin.
10:00–10:30 Degenerative Disease Accompanying Diabetes.
Dr. Hardin.
10:30–10:45 Intermission.
10:45–11:10 Management of the Person with Diabetes.
Dr. Lewis.
11:10–11:40 Management of Diabetes.
Dr. Hardin.
11:40–12:40 Lecture.
Dr. Gordon.
12:40– 2:00 Lunch.
P.M. Session
2:00– 3:00 Clinic Endocrine Cases.
Drs. Gordon, DeGowin, and Hardin.
3:00– 3:45 The Treatment of Arthritis.
Dr. Paul.
3:45– 4:00 Intermission.
4:00– 4:45 Dermatological Problems of Interest to the Internist. Cases will be presented.
Dr. Radcliffe.
4:45– 5:30 Clinical Pathological Conference.
Evening Session
Veteran's Hospital
7:30– 9:15 A program of short discussions, demonstrations and a question period.

Wednesday, June 20

A.M. Session
9:00– 9:45 A Practical Method of Maintenance of Fluid and Electrolyte Balance.
Dr. DeGowin.
9:45–10:30 Treatment of the Anemias.
Drs. Sheets and Hamilton.
10:30–10:45 Intermission.
10:45–11:45 Diagnosis and Treatment of Iron Deficiency Anemia.
Dr. Moore.
11:45–12:30 Treatment of the Leukemias and Related Diseases.
Dr. Fowler.
12:30– 2:00 Lunch.
P.M. Session
2:00– 2:45 Current Concepts of the Pathogenesis of Idiopathic Thrombocytopenic Purpura.
Dr. Moore.
2:45– 3:30 Coagulation Conference.
Moderator: Dr. Carter.
Drs. Warner, Jolly, and Hickey.
3:30– 3:45 Intermission.
3:45– 4:30 Osler's Disease.
Dr. Bean.
4:30– 5:30 Hematology Clinic.
Drs. Moore, Fowler, Sheets, and Hamilton.

Thursday, June 21

A.M. Session
9:00– 9:45 Physiologic Testing of Pulmonary Function.
Dr. Bedell.
9:45–10:30 Diagnosis and Treatment of Bronchial Asthma.
Dr. Seebohm.
10:30–10:45 Intermission.
10:45–11:15 Hyperventilation Syndromes—Clinical and Physiologic Features.
Dr. Lewis.

11:15–12:30	Round Table Conference on the Treatment of Pulmonary Tuberculosis. Moderator: Dr. Goldman. Drs. Spear, Horowitz, Gray and Smith.
12:30– 2:00	Lunch.
P.M. Session	
2:00– 3:00	Non-Tuberculous Granulomatous Lesions in the Chest. Dr. Goldman.
3:00– 3:30	Diagnosis and Treatment of Pulmonary Emphysema. Dr. Bedell.
3:30– 3:45	Intermission.
3:45– 4:30	Rare Diseases. Dr. Bean.
4:30– 5:30	Clinic—Chronic Pulmonary Disease. Drs. Goldman, Seebohm and Bedell.
Evening Session	
	Banquet—Jefferson Hotel.

Friday, June 22

A.M. Session	
9:00– 9:30	Infectious Hepatitis. Dr. Eckhart.
9:30–10:30	Round Table Conference—The Common Infectious Diseases. Moderator: Dr. Paul. Drs. Top and Smith.
10:30–10:45	Intermission.
10:45–11:15	Amebiasis. Dr. Hamilton.
11:15–12:00	Problems in the Treatment of Chronic Infection. Dr. Smith.
12:00–12:30	The Viral Encephalitides. Dr. Sahs.
12:30– 2:00	Lunch.
P.M. Session	
2:00– 2:45	Peptic Ulcer. Dr. Palmer.
2:45– 3:15	Diagnostic Methods in Gastro-enterology. Dr. Thornton.
3:15– 3:30	Intermission.
3:30– 4:15	Ulcerative Colitis—Round Table Conference. Moderator: Dr. Palmer. Drs. Thornton, Tidrick, and Lewis.
4:15– 5:00	Clinic—Gastro-intestinal Problems. Drs. Palmer, Thornton, Eckhardt and Ziffern.

Regional Meetings of the American College of Physicians

At the Los Angeles Annual Session of the College, the schedule and records of Regional Meetings held during 1955 and 1956, up to the date of the Session, were recorded as indicated hereafter. Regional Meetings are under the direction and administration of the College Governors in the several territories. Among the purposes of the Regional Meetings are: (1) to cement more closely acquaintanceships and interests of the local State groups; (2) to welcome new members and to provide them an opportunity to become better acquainted with the members in the territory; (3) in most instances to stimulate new members, particularly Associates, in giving many of them an opportunity to present papers; (4) to invite non-members interested in College membership thereby to provide them an opportunity to become known to the members of the College in their territories, and to stimulate such guests to fulfill the necessary requirements for Associateship.

Territory	City	Date	Governor(s)	Official Guest(s)	Registration		
					Mbrs.	Non-Mbrs.	Total
Ohio	Cleveland	Jan. 14	Charles A. Doan	Marion Blankenhorn E. R. Loveland	104	141	245
Colorado	Colorado Springs	Jan. 14–15	C. F. Kemper	Wm. H. Beierwaltes	60	89	149
Puerto Rico	San Juan	Jan. 28–29	Rafael Rodriguez-Molina	Ramon M. Suarez	22	41	63
Prairie Provinces (Man., Sask., Alta.)	Regina, Sask.	Feb. 4–5	Chas. H. A. Walton Percy C. Sprague	George F. Strong	28	31	59
Delaware	Wilmington	Feb. 5	Lemuel C. McGee	M. C. Pincoffs Thos. McMillan E. R. Loveland	48	79	127
Hawaii	Honolulu	Feb. 10	Nils P. Larsen	Wm. D. Stroud	26		26
Maryland-District of Columbia	Washington	Feb. 12	John Minor R. C. Tilghman	R. A. Kern M. C. Pincoffs	87	57	144
Southern California	San Diego	Feb. 12–13	Leland Hawkins	George F. Strong E. R. Loveland	144	76	220
Missouri	Columbia	Feb. 19	Carl V. Moore	M. A. Blankenhorn	51	27	78
Virginia	Lynchburg	Feb. 24	C. M. Caravati	Cyrus C. Sturgis	70	45	115
Nebraska	Omaha	Feb. 26	J. D. McCarthy	M. A. Blankenhorn E. R. Loveland	44	31	75
Utah	Salt Lake City	Mar. 5	T. C. Bauerlein	George F. Strong Fuller Bailey	21	31	52

1955 (continued)

Territory	City	Date	Governor(s)	Official Guest(s)	Registration		
					Mbrs.	Non-Mbrs.	Total
Kansas	Wichita	Mar. 18	W. C. Menninger	LeRoy H. Sloan	50	45	95
Southern Illinois	Peoria	Mar. 19	C. H. Drenckhahn	LeRoy H. Sloan	36	39	75
Tennessee	Chattanooga	Apr. 11	R. H. Kampmeier	S. A. Overstreet	41	9	50
West Virginia	White Sulphur Springs	Aug. 19	P. H. Revercomb	M. A. Blankenhorn	22	37	59
North Dakota	Jamestown	Sept. 10	Robert B. Radl	Wesley W. Spink	20	29	49
Montana-Wyoming	Billings, Mont.	Oct. 7–8	Harold W. Gregg	George F. Strong E. R. Loveland	19	13	32
Southeastern (Ala., Fla., Ga., S. C., Cuba)	Charleston, S. C.	Oct. 7–8	Robert Wilson William C. Blake Carter Smith D. O. Wright José Centurión		67	73	140
Western New York	Buffalo	Oct. 14	John H. Talbott	Walter L. Palmer	111	97	208
Midwest (Ill., Ind., Iowa, Minn., Wis.)	Madison, Wis.	Oct. 15	Frederick W. Madison James O. Ritchey C. H. Drenckhahn Wesley W. Spink Howard Wakefield Willis M. Fowler	Walter L. Palmer	164	119	283
Kentucky, Tennessee	Louisville, Ky.	Nov. 5	Rudolph H. Kampmeier Sam A. Overstreet	George F. Strong	71	36	107

1955 (continued)

Territory	City	Date	Governor(s)	Official Guest(s)	Registration		
					Mbrs.	Non-Mbrs.	Total
New Jersey	Newark	Nov. 9	Edward C. Klein, Jr.	George F. Strong George Morris Piersol E. R. Loveland George H. Lathrope Thomas M. McMillan Lemuel C. McGee	105	68	173
Western Pennsylvania	Pittsburgh	Nov. 10	Frank J. Gregg	John C. Gilson (England)	37	18	55
Ohio	Cincinnati	Nov. 17	Charles A. Doan	E. R. Loveland	80	79	159
Maryland-District of Columbia	Baltimore, Md.	Nov. 19	John Minor R. C. Tilghman	E. R. Loveland Richard A. Kern	102	99	201
Pacific Northwest (B. C., Ore., Wash.)	Vancouver, B. C.	Nov. 18–19	G. H. Anderson H. A. Des Brisay M. L. Margason	George F. Strong	49	14	63
Arkansas, Oklahoma	Hot Springs, Ark.	Dec. 3	Bert F. Keltz Arless A. Blair	E. R. Loveland Lemuel C. McGee	49	27	76
Michigan	Detroit	Dec. 3	H. Marvin Pollard	Walter L. Palmer	132	107	239
North Carolina	Winston-Salem	Dec. 8	Elbert L. Persons	E. R. Loveland	89	32	121
				TOTALS	1,949	1,589	3,538

1956

Territory	City	Date	Governor(s)	Official Guest(s)	Registration		
					Mbrs.	Non-Mbrs.	Total
Louisiana, Mississippi	Shreveport, La.	Jan. 4	Laurance J. Clark, Sr. M. D. Hargrove	Walter L. Palmer	52	46	98
Colorado	Colorado Springs	Jan. 20–21	C. F. Kemper	Walter L. Palmer	72	97	169
Eastern Pennsylvania	Philadelphia	Jan. 27	Thomas M. McMillan	Howard Sprague E. R. Loveland	200	140	340
Prairie Provinces (Man., Sask., Alta.)	Saskatoon, Sask.	Feb. 3–4	Charles H. A. Walton Percy H. Sprague	Walter L. Palmer	31	23	54
Arizona	Tucson	Feb. 4	Leslie R. Kober	Cyrus C. Sturgis	37	18	55
Virginia	Charlottesville	Feb. 23	Charles M. Caravati	Walter L. Palmer E. R. Loveland	108	56	164
Missouri	Columbia	Feb. 25	Carl V. Moore	J. Murray Kinsman	46	40	86
Nebraska	Lincoln	Mar. 3	Edmond M. Walsh	Edward L. Bortz	48	34	82
Hawaii	Honolulu	Mar. 6	Nils P. Larsen	George F. Strong	16	84	100
Kansas	Kansas City	Mar. 9	Wm. C. Menninger	William S. Middleton	47	46	93
Utah	Fort Douglas	Mar. 10	T. C. Bauerlein	Walter F. Palmer			*
Southern Illinois	Springfield	Mar. 24	C. H. Drenckhahn	Walter L. Palmer			*

* Attendance records not available at time of submission of this news item.

Postgraduate Courses in Pediatrics

A series of three postgraduate courses will be presented at the Children's Hospital in Philadelphia, May 28 through June 8. Course number one is "Pediatric Advances for Pediatricians and General Practitioners," May 28 through June 1. The second course is "Practical Pediatric Hematology," to be presented June 4–6. The third course is "Blood Group Incompatibilities and Erythroblastosis Fetalis," to be presented June 7–8. The tuition for these courses will be $100.00, $60.00 and $50.00, respectively, and any further information can be obtained from Irving J. Wolman, M.D., Children's Hospital of Philadelphia, 1740 Bainbridge St., Philadelphia 46, Pa.

Earl D. Osborne Fellowship

The American Academy of Dermatology and Syphilology announces the Earl D. Osborne Fellowship in Dermal Pathology. The Fellowship has a stipend of $4,000 a year divided into four quarterly payments during the year's fellowship. The award is primarily for postgraduate students who have completed at least one or two years of training in dermatology. The period of training will be spent at the Armed Forces Institute of Pathology in Washington, D. C., and the appointment is subject to the approval of the Director of the Institute. The next available appointment begins on July 1, 1957, and further information may be obtained from Dr. Hamilton Montgomery, Chairman of the Committee on Pathology of the American Academy of Dermatology and Syphilology, 200 First St., S.W., Rochester, Minn.

Eleventh Annual Schering Award Competition Opens

Students of medicine in the United States and Canada are invited to participate in submitting papers for the Award. The Award carries a $500 first prize and a $250 second prize. These are offered for each of the below-mentioned subjects.

1. The Clinical Use of Adrenocortical Steroids in Collagen Diseases.
2. Metabolic Aspects of the Aging Process.
3. New Applications of Antihistamines in Medicine and Surgery.

Students who are interested in participating, either individually or in teams, should submit their entry forms before July 1, 1956, and manuscripts must be postmarked not later than Sept. 30, 1956. Further information may be obtained from Mrs. Mary Campbell, Secretary, Schering Award Committee, Bloomfield, N. J.

Degrees in Biophysics

A graduate program in biophysics, which leads to either the M.S. or Ph.D. degree, has been established by the Sloan-Kettering Division of the Cornell University Medical College. The program is devoted primarily to radiation physics. There are extensive facilities in the Sloan-Kettering Institute and Memorial Hospital available for thesis problems in this field. Additional information on entrance requirements, courses, and program details may be obtained by writing to Dr. J. S. Laughlin, Department of Biophysics, 410 E. 68th St., New York 21, N. Y.

Public Health Service Research Grants

Statistics from the Public Health Service show that 3,036 research grants totaling $36,522,408 were issued between July 1, 1955, and January 1, 1956. The grants will aid research in medical schools, hospitals, and other non-Federal institutions through-

out the country. Dr. Leonard A. Scheele, F.A.C.P., stated that of the 3,036 grants, 634 were new—that is, awarded for the first time. The remaining grants were a continuation to support studies that had received similar funds during the previous year.

The awards are made on the recommendations of the National Advisory Councils, which is made up of seven councils and each composed of twelve non-Federal experts in medical science or public affairs, with an ex officio member from the Department of Defense and the Veterans Administration.

A closed-circuit live television clinic was telecast from Boston, Mass., Feb. 15. The telecast, entitled "Grand Rounds," originated in the Tufts University School of Medicine and the New England Medical Center, and was sponsored by The Upjohn Company. The theme of the telecast was "The Cardiac Patient In Stress: Work, Surgery, and Pregnancy." Acting as clinical leaders on the program were: Drs. C. Sidney Burwell, F.A.C.P., Harvard Medical School, Benjamin Etsten, Tufts University School of Medicine, Samuel A. Levine, F.A.C.P., Harvard Medical School, Samuel H. Proger, F.A.C.P., Tufts University School of Medicine, Merrill C. Sosman, Harvard Medical School, Paul Dudley White, M.A.C.P., Harvard Medical School.

Dr. William C. Menninger, F.A.C.P., College Governor for Kansas, acted as the moderator on a 90-minute television drama held on the CBS network March 18, entitled "Out of Darkness." Dr. Menninger is well known in the field of neuropsychiatry, having served as Director, Neuropsychiatric Consultants Division of the U. S. Army in World War II. The program was aimed at focusing public attention on mental illness, its causes and treatment. Dr. Menninger guided the television audience through modern treatment programs and the need for continuing research.

Five American medical scientists left this country recently for a four-weeks trip to Russia as representatives of the Public Health Service, Department of Health, Education, and Welfare. Of the five, two are members of the College, Drs. John R. Paul, F.A.C.P., Professor of Preventive Medicine, Yale University Medical School, New Haven, Conn., and Michael B. Shimkin, F.A.C.P., Chief of the Biometry and Epidemiology Branch, National Cancer Institute, Bethesda, Md. While in Russia they will visit various places of scientific interest and meet with Russian research scientists in their respective fields.

Dr. William B. Bean, F.A.C.P., Professor of Medicine, State University of Iowa, has recently been appointed to the Advisory Editorial Board of PHAROS, the AOA (Alpha Omega Alpha Honorary Medical Fraternity) Journal.

Dr. George M. Lewis, F.A.C.P., New York City, has recently been elected President of the American Academy of Dermatology and Syphilology.

Dr. Frank H. Krusen, F.A.C.P., Rochester, Minn., has been elected to the Presidency of the International Federation of Physical Medicine to succeed the late Dr. Thomas Jeeves (Lord) Horder. Dr. Krusen has been Head of the Section on Physical Medicine, Mayo Clinic, since 1935. Dr. Krusen will preside at the 1956 meeting to be held in Copenhagen, Denmark.

Drs. William A. Brams, Sidney Strauss and Julius H. Hess, all Fellows of the College, were recently presented with a bronze plaque for thirty years' service with the Michael Reese Hospital.

The American Heart Association has recently named Dr. F. Redding Hood, Sr., F.A.C.P., Oklahoma City, to its Board of Directors. Dr. Hood is a past President of his State organization.

Captain William M. Silliphant, (MC), USN, F.A.C.P., has recently accepted an appointment as a member of the Board of Editors of the *American Journal of Clinical Pathology*. The Journal is the official publication of the American Society of Clinical Pathologists. Captain Silliphant is presently Director of the Armed Forces Institute of Pathology, Washington, D. C.

Dr. Lowell T. Coggeshall, F.A.C.P., Assistant for Health and Medical Affairs, Department of Health, Education and Welfare, addressed the final dinner session of the National Health Council forum in New York City March 21–23. Dr. Coggeshall's address was entitled "America Can Meet the Challenge of Chronic Disease and Disability." Also participating in the program were Dr. Hugh R. Leavell, F.A.C.P., Boston, President, Dr. Theodore G. Klumpp, F.A.C.P., New York City, Vice President, who spoke on "Aims of the Forum," and Dr. Leonard A. Scheele, F.A.C.P., Washington, D. C., Surgeon General, Public Health Service, who acted as a moderator.

Rear Admiral Irwin L. V. Norman, (MC), USN, F.A.C.P., representing the Bureau of Medicine and Surgery, presented a paper at the Mid-Atlantic Section Meeting of the International College of Surgeons at White Sulphur Springs, W. Va., on Feb. 14. Admiral Norman's paper was entitled "The Personnel Situation of the Medical Department of the U. S. Navy."

Dr. Benjamin B. Wells, F.A.C.P., Omaha, Professor of Medicine at the Creighton University School of Medicine, was a guest speaker at the annual meeting of the Sioux Valley Medical Society held in Sioux City, Iowa, Feb. 22–23. Dr. Wells gave talks on "Acute Renal Failure" and "Indications for Splenectomy."

The annual meeting of the American Psychosomatic Society was held in Boston, March 24–25. Harold G. Wolff, M.D., F.A.C.P., New York City, served as the Chairman in the discussion entitled "Contributions from Sociology," and Drs. Harry Shay, F.A.C.P., and Edward Weiss, F.A.C.P., both of Philadelphia, took an active part in presenting "Psycho-physiological Studies of Gastric Secretion in a Case of Peptic Ulcer."

Dr. Leo H. Criep, F.A.C.P., Pittsburgh, Pa., addressed the medical staff and guests of the Gorgas Hospital, Canal Zone, Panama, on the subject of "Allergy—Clinical and Pathologic Consideration," March 2.

Dr. Ralph Emmett Porter, F.A.C.P., is the Director of the Sixth District Tuberculosis Hospital recently dedicated at Mobile, Ala. This new hospital represents three years of extremely hard work by citizens from six Southwest Alabama Counties. The building was dedicated by U. S. Senator Lister Hill of Alabama.

The second annual seminar in Gastroenterology was presented by the medical staff of Huron Road Hospital in Cleveland on March 27–28. On the program were Henry G. Rudner, Jr., M.D., (Associate), Memphis, Tenn., Charles M. Thompson, M.D., F.A.C.P., Philadelphia, Pa., Seymour J. Gray, M.D., F.A.C.P., Boston, Mass., Arthur M. Olsen, M.D., F.A.C.P., Rochester, Minn., and Abraham H. Aaron, M.D., F.A.C.P., Buffalo, N. Y.

A conference on experimental methods for the evaluation of drugs was held March 8–9 by the New York Academy of Sciences at the Barbizon-Plaza Hotel in New York. Topics discussed included angina pectoris, disorders of the central nervous system and collagen diseases. Participating actively were Louis N. Katz, M.D., F.A.C.P., Chicago, Wilhelm Raab, M.D., F.A.C.P., Burlington, Vt., and Luther L. Terry, M.D., F.A.C.P., Bethesda, Md.

Dr. M. Eugene Flipse, F.A.C.P., Miami, Fla., has recently been released from the U. S. Navy with the rank of Commander. Dr. Flipse is now associated with the full-time faculty of the University of Miami School of Medicine as Assistant Professor of Medicine.

Attention is directed to the appearance recently of a new French journal devoted to the publication of clinical and biological studies, *Revue Française d'Études Cliniques et Biologiques*. Appearing under the sponsorship of a distinguished group of French scientists, it will be welcomed by American investigators and clinicians. Publishers are Flammarion, 22. Rue de Vaugirard, Paris.

Georg Thieme Verlag of Stuttgart have inaugurated in January 1956 publication of a monthly English language edition of the *Deutsche medizinische Wochenschrift*, to be known as the *German Medical Journal*.

COMING EVENTS, 1956

May 28–June 1	First International Symposium on Venereal Diseases and the Treponematoses, under joint sponsorship of the U. S. Public Health Service and the World Health Organization, Statler Hotel, Washington, D. C.; Dr. C. A. Smith, Medical Director, Division of Special Health Services, Department of Health, Education and Welfare, Washington 25, D. C.
June 4–6	American Cancer Society-National Cancer Institute, U. S. Public Health Service, Detroit, Mich.; National Cancer Conferences Coördinator, American Cancer Society, 521 W. 57th St., New York 19, N. Y.
June 7–10	American College of Chest Physicians, Chicago, Ill.; Mr. Murray Kornfeld, Secretary, 112 E. Chestnut St., Chicago 11, Ill.

June 9–10	American Diabetes Association, Chicago, Ill.; Dr. F. B. Peck, Sr., 1 E. 45th St., New York 17, N. Y.
June 9	American Academy of Tuberculosis Physicians, Chicago, Ill.; Dr. Oscar S. Levin, Secretary, P. O. Box 7011, Denver 6, Colo.
June 10–11	American Gastroscopic Society, Chicago, Ill.; Dr. C. Wilmer Wirts, Secretary-Treasurer, 1025 Walnut St., Philadelphia 7, Pa.
June 10–14	Canadian Medical Association, Quebec, Canada; Dr. Arthur D. Kelly, Secretary, 150 St. George St., Toronto 5, Ont., Can.
June 11–15	American Medical Association, Chicago, Ill.; (Clinical Session, Nov. 27–30, Seattle, Wash.); Dr. George F. Lull, Secretary, 535 N. Dearborn St., Chicago 10, Ill.
June 18–21	American Dermatological Association, Santa Barbara, Calif.; Dr. J. Lamar Callaway, Secretary, Duke Hospital, Durham, N. C.
June 18–20	American Neurological Association, Atlantic City, N. J.; Dr. Charles Rupp, Secretary, 133 S. 36th St., Philadelphia 4, Pa.

OBITUARIES

RECENT DEATHS OF A.C.P. MEMBERS

The College records with sorrow the deaths of the following members. Their obituaries will appear later in these columns.

Dr. Joseph Lettenberger, F.A.C.P., Milwaukee, Wis., Nov. 1, 1955
Dr. Clovis Litle McKibben, F.A.C.P., Ontario, Calif., Jan. 21, 1956
Dr. Ralph Bowen, F.A.C.P., Houston, Tex., Jan. 31, 1956
Dr. Malcolm Thomas MacEachern, F.A.C.P., Chicago, Ill. Feb. 3, 1956
Capt. Paul White Wilson, (MC), USN, (Ret'd), F.A.C.P., Los Angeles, Calif., Feb. 15, 1956
Dr. John Olen Woods, F.A.C.P., New Castle, Pa., Feb. 17, 1956
Dr. (Mary) Elizabeth Bass, F.A.C.P., Lumberton, Miss., January 26, 1956
Dr. Joseph H. Pratt, F.A.C.P., Boston, Mass., March 3, 1956
Dr. William Egbert Robertson, F.A.C.P., Phila., Pa., March 9, 1956

DR. OSCAR B. RAGINS

Dr. Oscar Benjamin Ragins, F.A.C.P., died of heart disease on Nov. 18, 1955, in Chicago, Ill. Dr. Ragins was born in Loef, Russia, on Aug. 20, 1893. He came to Chicago when he was nineteen years old and studied medicine at the University of Illinois, where he received his M.D. degree from the College of Medicine in 1921.

He served an internship at Michael Reese Hospital from 1921–23. He joined the faculty of his alma mater as a Clinical Assistant in 1928 and served in various ranks until he became Associate Professor of Clinical Medicine in 1942. Dr. Ragins had served the Cook County Graduate School of Medicine as Professor of Clinical Medicine since 1939.

At the time of his death, Dr. Ragins was the Head Physician of the Municipal Tuberculosis Sanitarium Clinic at Provident Hospital in Chicago. He also served as Attending Physician to the Cook County Hospital and Mount Sinai Hospital.

Dr. Ragins became a Fellow of the American College of Physicians in 1953 and in 1954 a Life Member of the College. He was a member of the Chicago Medical Society, Chicago Tuberculosis Society, Illinois State Medical Society, the American Medical Association, and the Israel Medical Society. He was a Diplomate of the American Board of Internal Medicine.

During his entire professional life, he was always interested in and was an ardent worker in the field of tuberculosis. For many years he maintained an effective program of undergraduate teaching at Illinois. He was active in the cultural and civic affairs in his community. His family, friends, and patients will miss him.

He is survived by his widow, Ida, who lives at 5240 Greenwood Ave., Chicago 15.

HOWARD WAKEFIELD, M.D., F.A.C.P.,
Governor for Northern Illinois

IMPORTANT RESEARCH CONTRIBUTION

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Investigations with Nilevar show that nitrogen, potassium and phosphorus are retained in ratios indicating protein anabolism. Nilevar is thus the first steroid which is primarily anabolic and which provides a practical means of meeting the numerous demands for protein synthesis.

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DOSAGE • The daily *adult* dose is three to five Nilevar tablets (30 to 50 mg.) but up to 100 mg. may be administered. For *children* the daily dose is 1 to 1.5 mg. per kilogram of body weight. Individual dosages depend on need and response to therapy. Nilevar is available in 10 mg. tablets. G. D. Searle & Co., Research in the Service of Medicine.

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6. **Domiciliary care of decubitus ulcers.**
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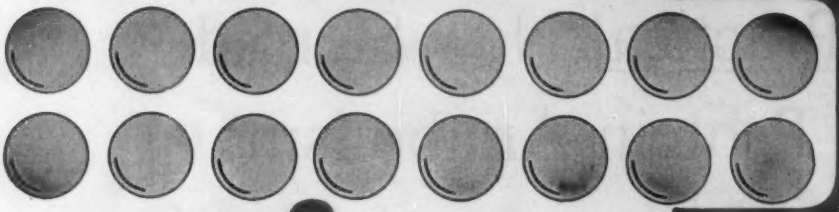

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Antibiotic A	71.4	55.5	25.0	93.5	96.9	66.0	26.6
Dihydrostreptomycin	14.2	25.9	12.5	38.7	27.2	28.0	6.6
Antibiotic B	3.5	0	0	66.1	63.6	0	2.2
Penicillin	3.5	0	0	27.4	39.3	0	0
Antibiotic C	14.2	7.4	18.7	46.7	72.6	22.0	11.1

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Oral Suspension, 5 mg. per cc., bottle of 118 cc.

REFERENCES: 1. Waisbren, B. A., and Crowley, W.: A.M.A. Arch. Int. M. 95:653, 1955. 2. Perry, R. E., Jr.: North Carolina M. J. 16:567, 1955.

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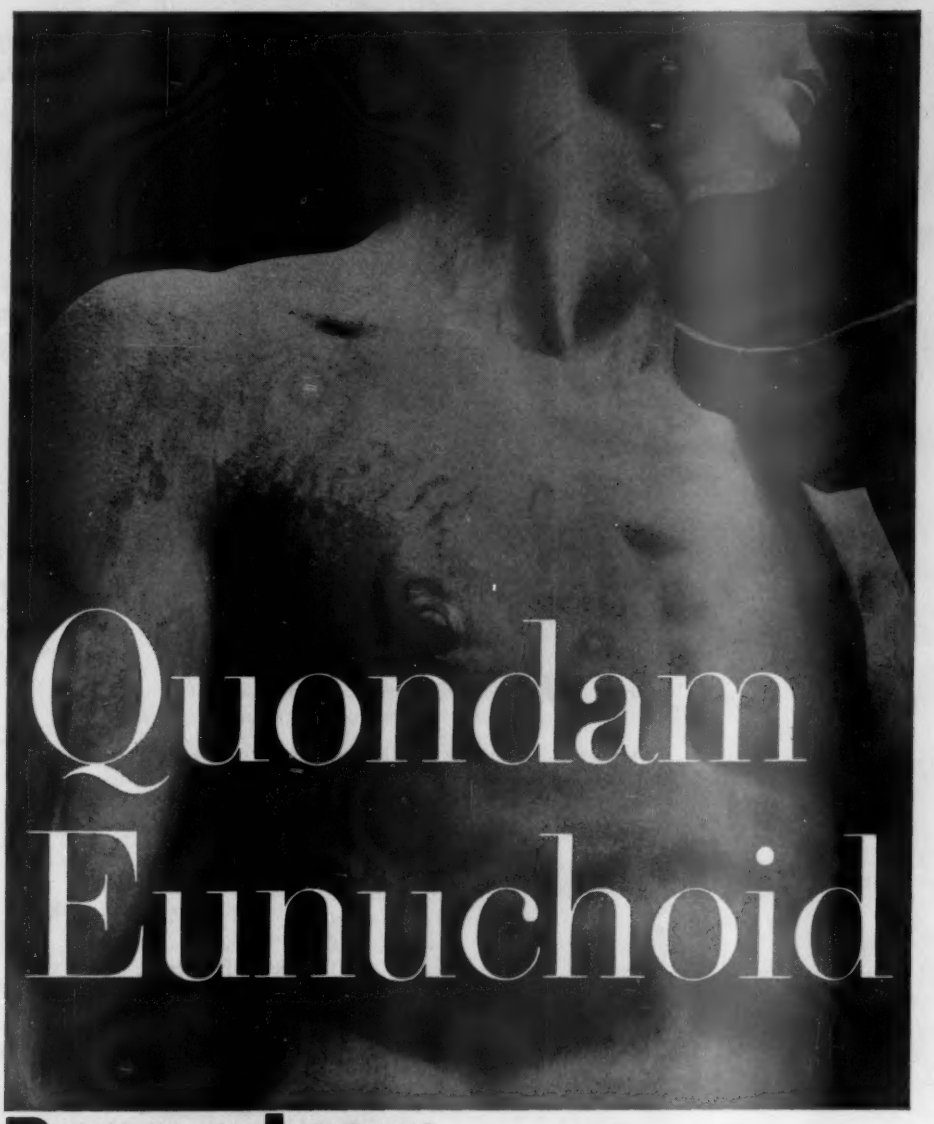

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Multiple-dose Vials, 10 ml., each ml. containing 50 mg. Perandren phenylacetate (with 1% procaine hydrochlorides).

9/222608

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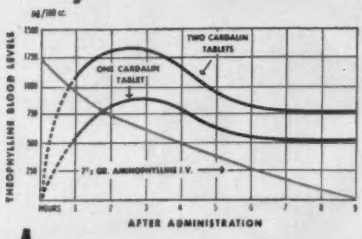

Sustained theophylline blood levels were higher with 1 or 2 oral Cardalin tablets than with 7½ gr. of aminophylline I.V.

(Adapted from Bickerman, H. A., et al.: Ann. Allergy 11:301, 1953, and Truitt, E. B., Jr., et al.: J. Pharmacol. & Exper. Therap. 100:309, 1950.)

to produce therapeutic results

When the asthmatic gasps for air...

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Each Cardalin tablet supplies:

Aminophylline .... 5.0 gr.
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Excellent increases in vital capacity and maximum breathing capacity.

Bickerman, H. A., et al.: Ann. Allergy 11:309, 1953.

Produces productive coughing following bronchodilatation.

Barach, A. L., et al.: Dis. of Chest 23:121, 1953.

Continued relief of paroxysms of bronchospasm.

Segal, M. S., et al.: Quart. Rev. Allergy & Applied Immunol. 6:399, 1952.

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dosage:

Adults: One green 60 mg. capsule daily or one to three orange 20 mg. capsules daily.

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1. Wilson, J. L., and Dickinson, D. C.: J.A.M.A. *158*:261 (May 28) 1955.

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*Patent Pending

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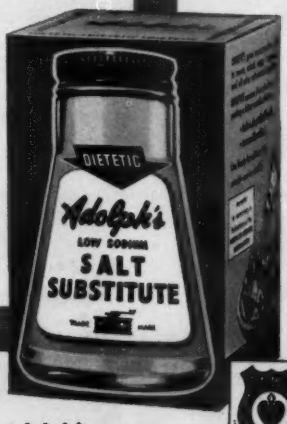

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1. Chamberlain, D. T., Gastroent. 17:224-5, 1951. 2. McHardy, G., and Bevans, D. C., South. M.J. 45:1139, 1952. 3. Pasulis, S. F., Postgrad. Med. 11:123, 1952.

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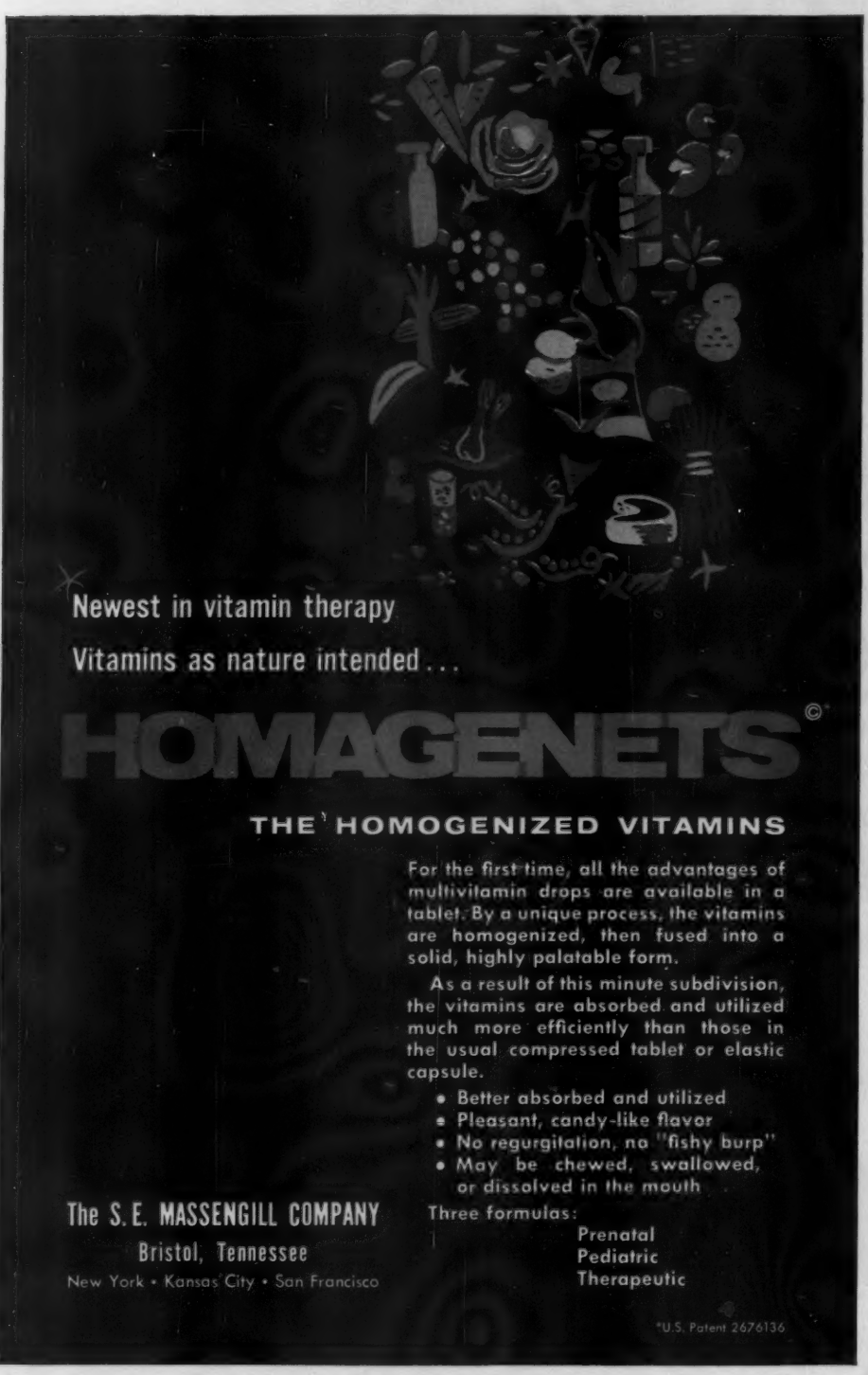
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establishing
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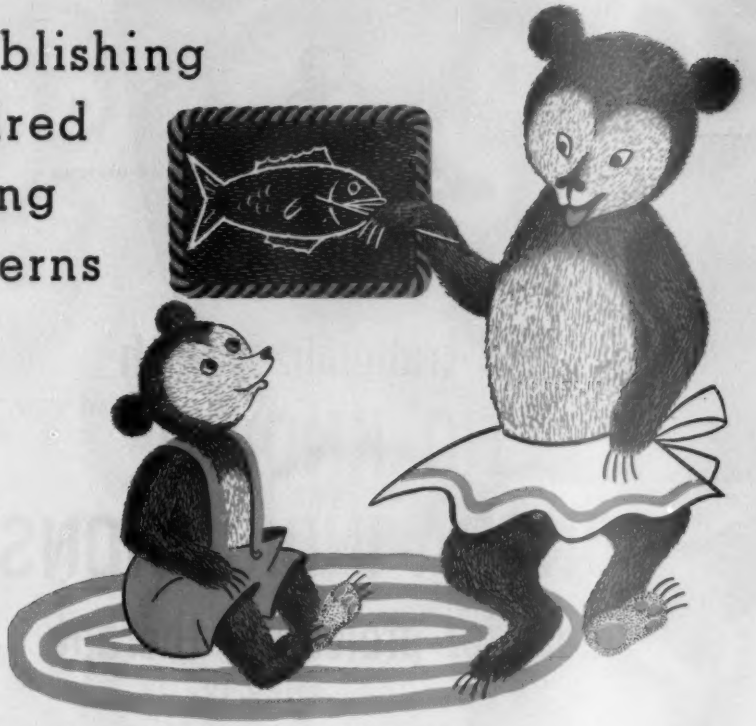

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In the development of good eating habits, medication is important, not only in initiating control, but also in maintaining normal weight.[1,2,3]

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1. Eisfelder, H.W.: Am. Pract. & Dig. Treat., 5:778 (Oct.) 1954).
2. Sebrell, W.H., Jr.: J.A.M.A., 152:42 (May, 1953).
3. Sherman, R.J.: Medical Times, 82:107 (Feb., 1954).

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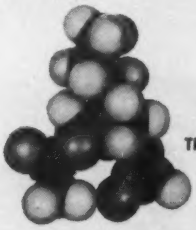

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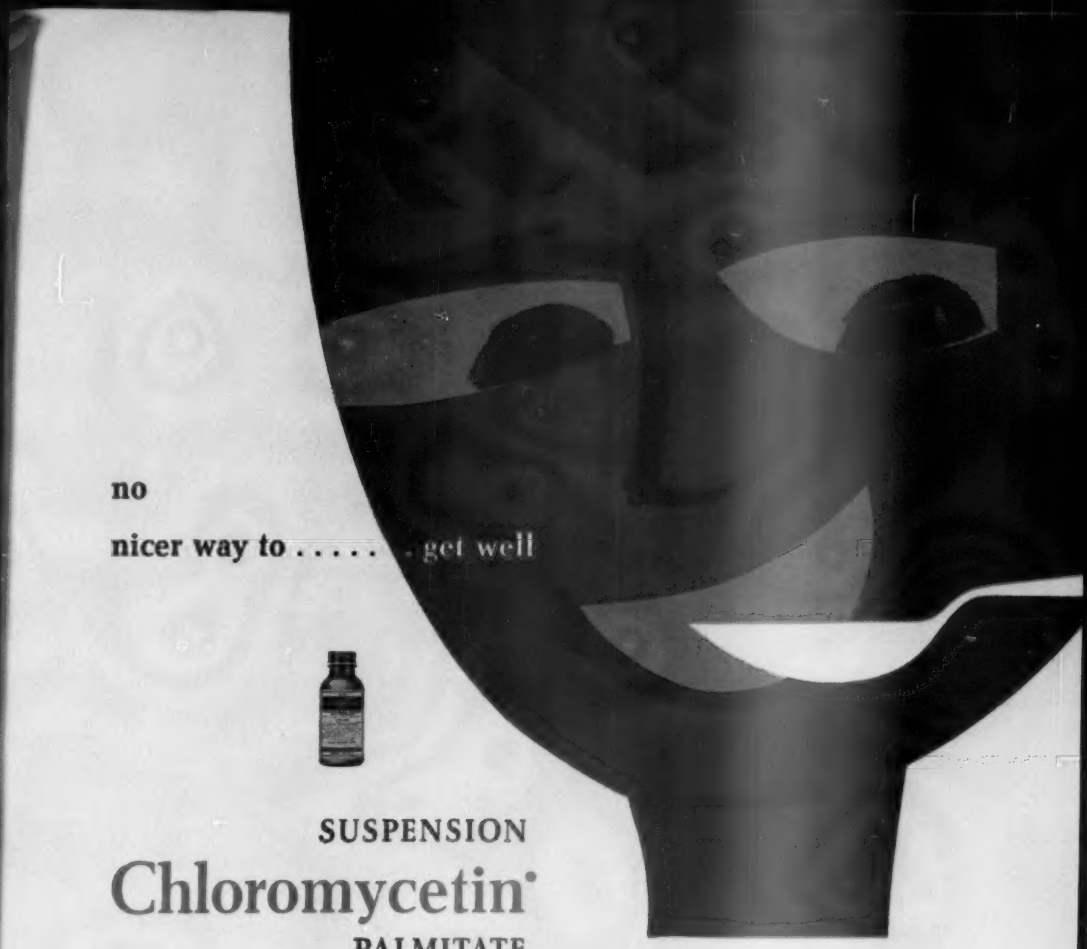

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pleasant-tasting CHLOROMYCETIN for pediatric use

When a youngster's condition calls for CHLOROMYCETIN (chloramphenicol, Parke-Davis) you can make the treatment pleasant by prescribing SUSPENSION CHLOROMYCETIN PALMITATE. Because children like the taste of this custard-flavored suspension, missed doses and spilled doses are avoided. Each teaspoonful is willingly taken... and swallowed. Precise adjustment of dosage, as directed, is made easier for the child's mother with SUSPENSION CHLOROMYCETIN PALMITATE. The fact that it needs no refrigeration is an added convenience.

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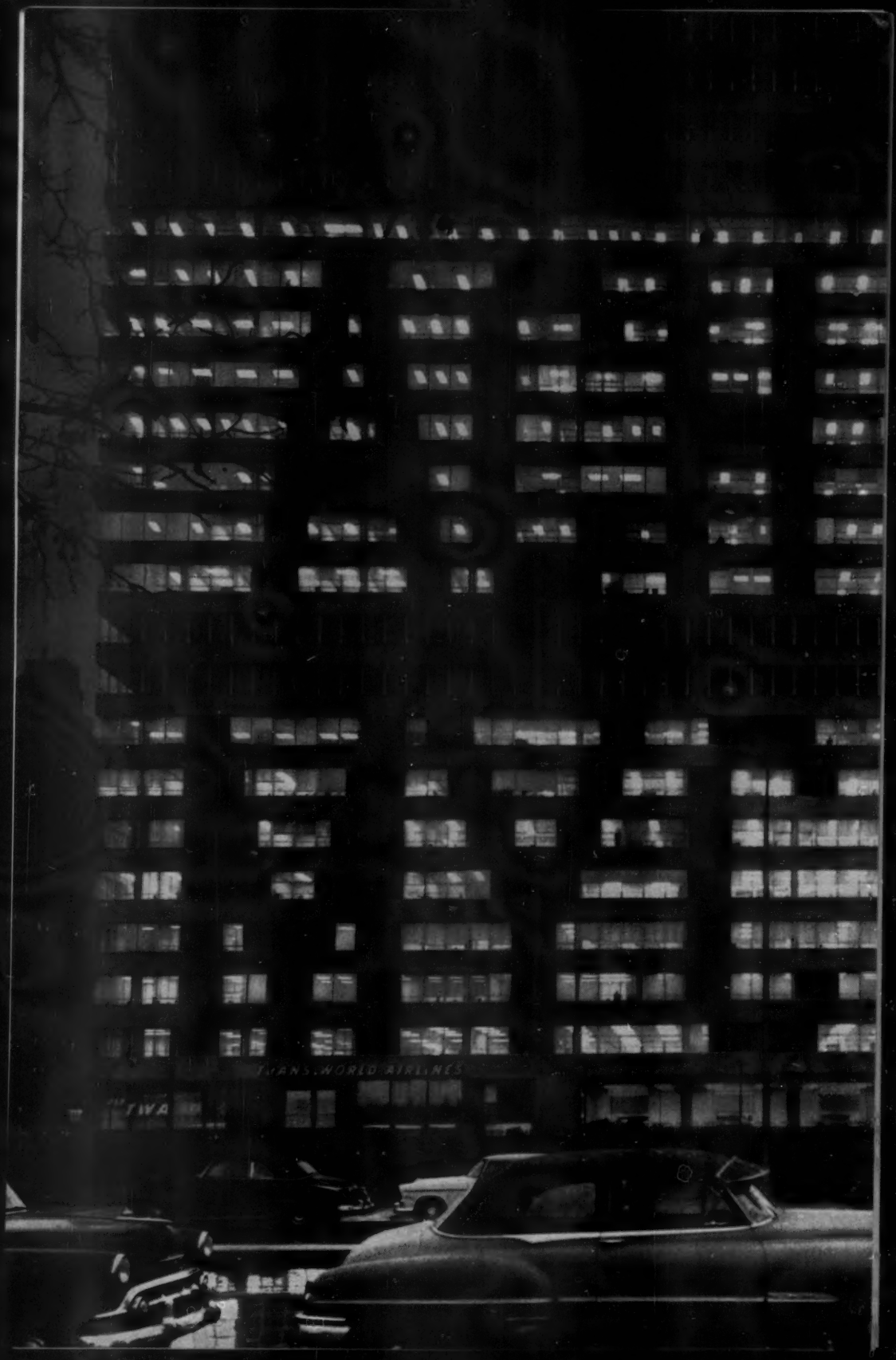
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In the treatment of

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January and his associates[1] have written on the use of tetracycline (ACHROMYCIN) to treat 118 patients having various infections, most of them respiratory, including acute pharyngitis and tonsillitis, otitis media, sinusitis, acute and chronic bronchitis, asthmatic bronchitis, bronchiectasis, bronchial pneumonia, and lobar pneumonia. Response was judged good or satisfactory in more than 84% of the total cases.

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[1]January, H. L. et al: Clinical experience with tetracycline. *Antibiotics Annual* 1954-55, p. 625.

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is easier with STERANE[1]—3-5 times more active than hydrocortisone or cortisone.[2]

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WITH MINIMAL DISTURBANCE
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brand of prednisolone

supplied: *White, 5 mg. oral tablets, bottles of 20 and 100. Pink, 1 mg. oral tablets, bottles of 100.*

1. Spies, T. D., et al.: GP 12:73, No. 1, 1955. 2. Boland, E. W.: J.A.M.A. 160:613, 1956. 3. Gillhespy, R. O.: Lancet 2:1393, 1955.

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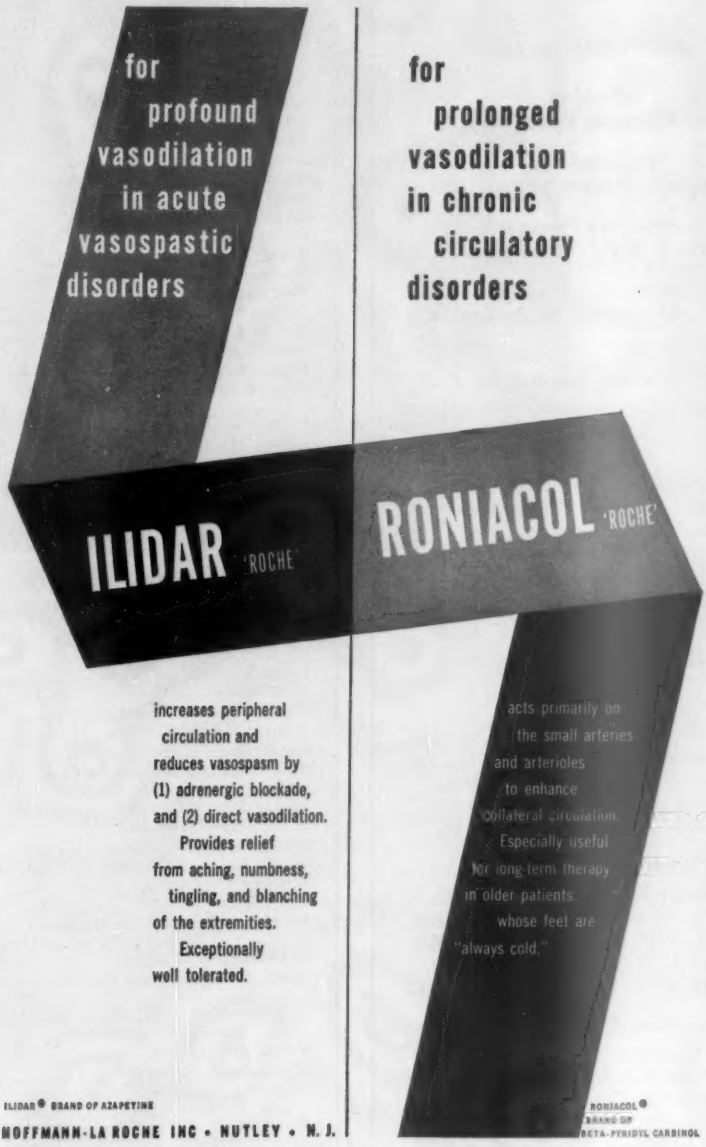
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in acute
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from aching, numbness,
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Reduces Muscular Tension

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MEPROBAMATE
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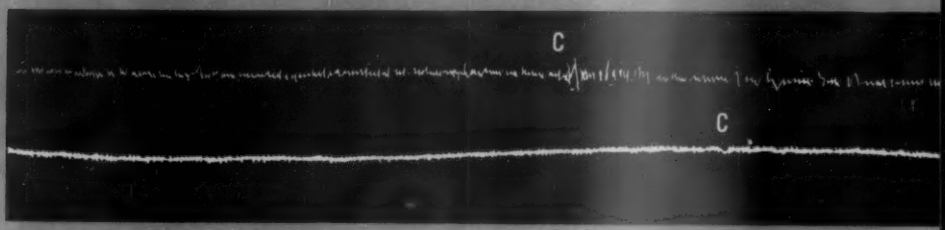
Licensed under U.S. Patent No. 2,724,720

Electromyography shows decisive response



Electromyographic study of neuromuscular hyperactivity in 42-year-old male with anxiety-tension syndrome. A, Before EQUANIL; action potential of high amplitude and frequency. B, After one week of ambulatory treatment with EQUANIL; showing definite reduction in tension, greater ability to relax, and marked improvement in muscular coordination. C, Point where patient makes effort to relax.[1]

The remarkable effectiveness of EQUANIL may be demonstrated in two ways. One is by its ability to relieve muscle spasm and neuromuscular tension.[1] The second is by its ability to relieve mental tension and anxiety.

Usual dosage: 1 tablet t.i.d. The dose may be adjusted either up or down, according to the clinical response of the patient.

Supplied: Tablets, 400 mg., bottles of 50.

1. Dickel, H.A., et al.: West. J. Surg. *64*:197 (April) 1956

anti-anxiety factor with muscle-relaxing action . . . relieves tension

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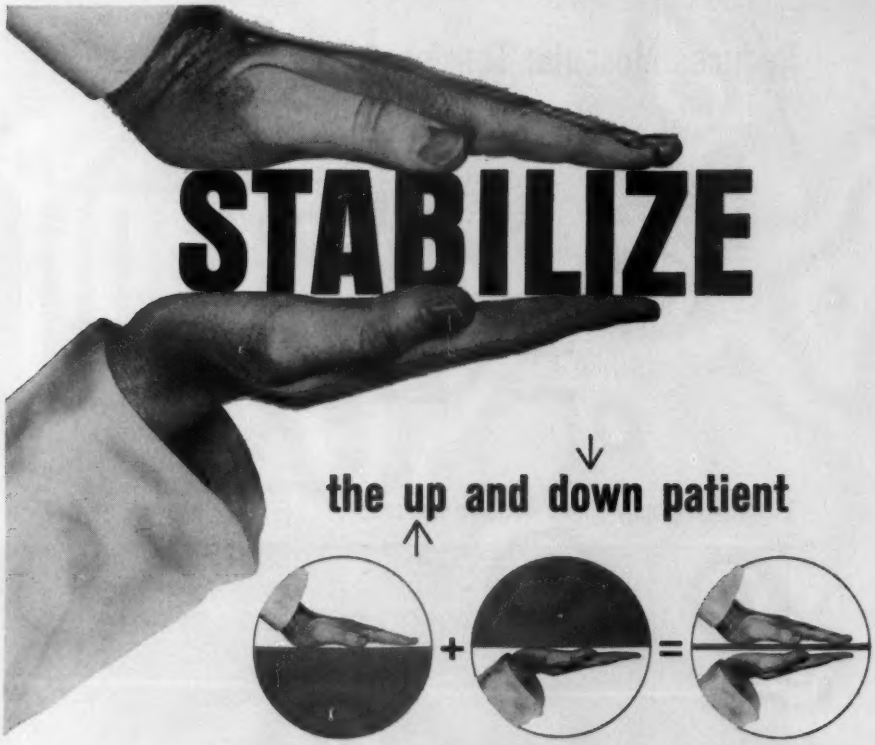

To induce emotional equilibrium in those who swing from anxiety to depression, Serpatilin combines the relaxing, tranquilizing action of Serpasil with the mild mood-lifting effect of the new cortical stimulant, Ritalin. In recent months, numerous clinical studies have indicated the value of combining these agents for the treatment of various disorders marked by tension, nervousness, anxiety, apathy, irritability and depression. Arnoff,[1] in a study of 51 patients, found the combination of definite value in a variety of complaints, noting no effect on blood pressure or heart rate. Lazarte and Petersen[2] also found Serpatilin effective in counteracting the side effects of reserpine and chlorpromazine. They reported: "The stimulating effect of Ritalin seemed complementary to the action of reserpine . . . in that it brought forth a better quality of increased psychomotor activity."

1. Arnoff, B.: Personal communication. 2. Lazarte, J. A., and Petersen, M. C.: Personal communication.

Serpatilin Tablets, 0.1 mg./10 mg., each containing 0.1 mg. Serpasil® (reserpine CIBA) and 10 mg. Ritalin® hydrochloride (methyl-phenidylacetate hydrochloride CIBA).

Dosage: 1 tablet b.i.d. or t.i.d., adjusted to the individual.

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SUMMIT, N. J.

Serpatilin T.M.

(reserpine and methyl-phenidylacetate hydrochloride CIBA)

2/22809M

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4. Doe, J. E.: What I know about it, J. A. M. A. 98: 2006, 1931.

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